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(54) Title: AVB3 AND AVB5 INTEGRIN ANTAGONISTS AND METHODS OF TREATING DISEASES OR CONDITIONS ASSOCIATED WITH AVB3 AND AVB5 INTEGRINS

(57) Abstract: This invention relates to compounds having the formula (I) wherein w, x, y, D, L, Q, R, R^7 and R_{11} are as defined in the specification. The compounds habe been found to be $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ integrin antagonists. Pharmaceutical compositions containing the compounds, methods of making them, and methods of treatment of conditions associated with the $\alpha_v\beta_3$ integrin or $\alpha_v\beta_5$ integrin by administering a therapeutically effective amount of the compounds are also described.

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$\alpha_v\beta_3$ and $\alpha_v\beta_5$ Integrin Antagonists and Methods of Treating Diseases or Conditions Associated with $\alpha_v\beta_3$ and $\alpha_v\beta_5$ Integrins

DESCRIPTION OF THE INVENTION

The present invention relates to:

(1) compounds described by formula (I) or purified stereoisomers or stereoisomer mixtures, or their salts or prodrug forms thereof;

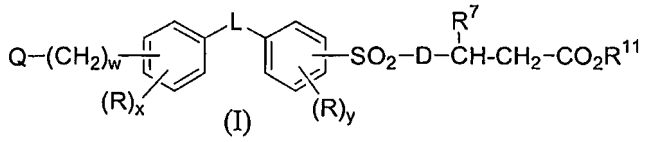
(2) pharmaceutical compositions comprising one or more of the compounds of formula (I) or purified stereoisomers or stereoisomer mixtures of (I), or their salts or prodrug forms, with a pharmaceutically acceptable ingredient;

(3) methods for preparing the compounds of formula (I); and

(4) a method of treating diseases or conditions associated the $\alpha_v\beta_3$ integrin and/or $\alpha_v\beta_5$ integrin by administering a therapeutically effective amount of the compound of formula (I) to a patient in need thereof.

Description of the Compounds

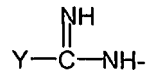
The compounds described as being part of the invention have the structural formula (I) defined below:



(I)

wherein:

Q is a substituent selected from the group consisting of:

(a) 

wherein

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_3-C_5-alkenyl,

(a5) C_4-C_8-cycloalkenyl,

(a6) C_3-C_5-alkynyl,

(a7) C_6-C_{10}-aryl,

(a8) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(a9) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(a10) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

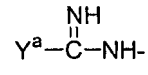
(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and $-NZ^1Z^2$; and

(a2) - (a10) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or $-NZ^1Z^2$, wherein

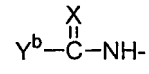
Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

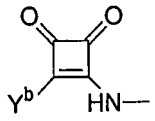
Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

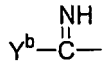
(b) 

wherein Y^a represents $-NH_2$ or -NH-Y;

(c) 

wherein X represents O, S or N(CN) ;

(d) 

(e) 

wherein for (c) - (e)

Y^b represents $-NH_2$, -NH-Y or -Y;

(f) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(f1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(f2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(f2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(f2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (f1) - (f2) are optionally substituted by R;

(g) Y^c=N-

wherein Y^c is as defined in (f) above;

(h) Y^dY^e-N-

wherein Y^d and Y^e are independently selected from the group consisting of hydrogen, C_1-C_5-alkyl, and C_1-C_5-aminoalkyl;

and

(i) when w = 0, Q forms a four to eight membered heterocyclic ring fused to the aryl group to which it is attached to form a bicyclic ring, wherein said heterocyclic ring contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and at least one carbon atom and said heterocyclic ring is optionally substituted with C_1-C_5-alkyl or $-NZ^3Z^4$ wherein Z^3 and Z^4 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1,

(g) $C(=O)OR^1$,

(h) $S(=O)_2OR^1$,

(i) NR^1R^2,

(j) $C(=O)NR^1R^2$, and

(k) $S(=O)_2NR^1R^2$;

wherein for (f)-(k):

R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

or

wherein for (i)-(k):

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) O,

(b) C(=O),

(c) CR^3R^4,

(d) $N(R^5)$,

(e) $S(=O)_z$,

(f) $C(=O)N(R^5)$,

(g) $N(R^5)C(=O)$,

(h) $S(=O)_2N(R^5)$

(i) $N(R^5)S(=O)_2$,

(j) CR^3R^4-CR^3R^4,

(k) CH_2O,

(l) OCH_2,

(m) $CH_2N(R^5)$,

(n) $N(R^5)CH_2$,

(o) CH=CH,

(p) -C≡C- ; and

(q) $C(=NR^3)$

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) C_1-C_3-alkyl, and

(4) C_1-C_3-alkoxy;

wherein:

when one or two R^3 groups are C_1-C_3-alkyl in L, said one or two R^3 groups may constitute spiro rings or nonspiro rings wherein:

(a) one group R^3 is joined by a bond or by a heteroatom selected from the group consisting of oxygen, nitrogen and sulfur, to the carbon chain to which said group R^3 is attached, and taken together with the carbon chain atom(s) to which said group R^3 is attached, constitutes a ring of three to six members,

wherein for CR^3R^4, when R^3 is C_1-alkyl, the R^3 group is joined by a heteratom as defined above, or

(b) two groups R^3 are joined by a bond or by a heteroatom selected from the group consisting of oxygen, nitrogen and sulfur and taken together with the carbon chain atom(s) to which said two groups R^3 are attached, constitute a ring of 3-6 members; or

R^5 represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

D represents a substituent selected from the group consisting of:

(a) $(CH_2)_v$ and

(b) $N(R^6)$

wherein R^6 represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

and wherein:

L is not $C(=O)N(R^5)$, $N(R^5)C(=O)$, $S(=O)_2N(R^5)$ or $N(R^5)S(=O)_2$- when D is -NH-;

R^7 represents a substituent selected from the group consisting of:

(a) C_2-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_2-C_5-alkynyl,

where (a)-(f) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (g)-(j) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_2OH$,

(5) $S(=O)_nR^{10}$,

(6) $S(=O)_2NR^8R^9$,

(7) NR^8R^9,

(8) OR^8,

(9) $C(=O)R^{10}$,

(10) $C(=O)OR^8$; or

(11) $C(=O)NR^8R^9$;

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (g) – (j) are substituted by NR^8R^9, $S(=O)_2NR^8R^9$ or $C(=O)NR^8R^9$,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl;

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_3-C_5-alkynyl,

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (a)-(j) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl,

(c) C_3-C_6-cycloalkyl,

(d) C_3-C_6-alkenyl,

(e) C_5-C_6-cycloalkenyl, and

(f) C_3-C_6-alkynyl

wherein (b)-(f) are optionally substituted by:

(1) halogen,

(2) OR^{12}, or

(3) $NR^{12}R^{13}$;

wherein

R^{12} and R^{13} independently represent hydrogen or C_1-C_3-alkyl;

or

R^{12} and R^{13} together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

u is an integer from 0 - 2;

v is an integer from 1 - 2;

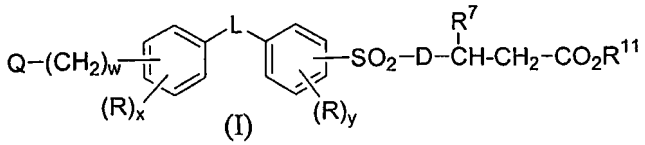
n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

Alternative embodiments

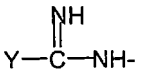
In one embodiment, the compounds of the invention are sulfonamides having the formula



(I)

in which D is NH and the various other groups and units are preferably defined as follows:

Q is a substituent selected from the group consisting of:

(a) 

wherein

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_4-C_8-cycloalkenyl,

(a5) C_6-C_{10}-aryl,

(a6) C_6-C_{10}-aryl-C_1-C_3-alkyl, and

(a7) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and -NZ^1Z^2; and

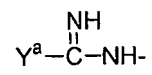
(a2) - (a7) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or -NZ^1Z^2,

wherein

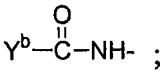
Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

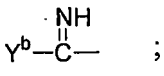
or

Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

(b) 

wherein Y^a represents -NH_2 or -NH-Y;

(c)  ;

(d)  ;

wherein for (c) - (d)

Y^b represents $-NH_2$, -NH-Y or -Y;

(e) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(e1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(e2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(e2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(e2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (e1) - (e2) are optionally substituted by R;

(f) Y^c=N-

wherein Y^c is as defined in (e) above;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1, and

(g) NR^1R^2,

wherein for (f) and (g), R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, and

(3) C_3-C_8-cycloalkyl;

or

wherein for (g), R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) CR^3R^4-CR^3R^4,

(b) CH_2O,

(c) OCH_2,

(d) CH=CH, and

(e) -C≡C- ;

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_3-alkyl, and

(3) C_1-C_3-alkoxy;

D represents NH;

R^7 represents a substituent selected from the group consisting of:

(a) C_3-C_8-cycloalkyl,

(b) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(c) C_3-C_5-alkenyl,

(d) C_4-C_8-cycloalkenyl,

(e) C_2-C_5-alkynyl,

where (a)-(e) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(f) C_6-C_{10}-aryl,

(g) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(h) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(i) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (f)-(i) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_nR^{10}$,

(5) NR^8R^9,

(6) OR^8, or

(7) $C(=O)R^{10}$,

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (f) – (i) are substituted by NR^8R^9,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl; and

wherein (a)-(c) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl,

(c) C_3-C_6-cycloalkyl,

(d) C_3-C_6-alkenyl,

(e) C_5-C_6-cycloalkenyl, and

(f) C_3-C_6-alkynyl

wherein (b)-(f) are optionally substituted by:

(1) halogen, or

(2) OR^{12},

wherein

R^{12} represents hydrogen or C_1-C_3-alkyl;

u is an integer from 0 - 2;

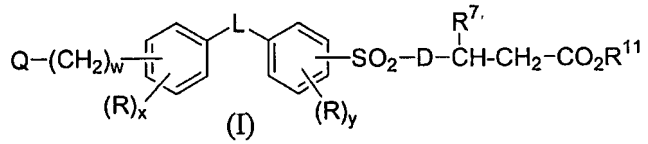
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

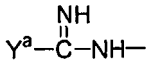
In another embodiment, the compounds of the invention are sulfonamides having the formula



(I)

in which D is NH and the various groups and units are more preferably defined as follows:

Q is a substituent selected from the group consisting of:

(a) 

wherein

Y^a represents $-NH_2$ or -NH-Y; and

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_4-C_8-cycloalkenyl,

(a5) C_6-C_{10}-aryl,

(a6) C_6-C_{10}-aryl-C_1-C_3-alkyl, and

(a7) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and $-NZ^1Z^2$; and

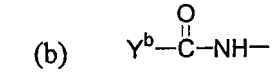
(a2) - (a7) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or $-NZ^1Z^2$,

wherein

Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

(b) 

wherein Y^b represents $-NH_2$, -NH-Y or -Y;

(c) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(c1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(c2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(c2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(c2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (c1) - (c2) are optionally substituted by R;

(d) Y^c=N-

wherein Y^c is as defined in (c) above;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1, and

(g) NR^1R^2,

wherein for (f) and (g), R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, and

(3) C_3-C_8-cycloalkyl;

or

wherein for (g), R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) CR^3R^4-CR^3R^4,

(b) CH_2O, and

(c) OCH_2,

R^3 and R^4 each independently represents H;

D represents NH;

R^7 represents a substituent selected from the group consisting of:

(a) C_3-C_8-cycloalkyl,

(b) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(c) C_3-C_5-alkenyl,

(d) C_4-C_8-cycloalkenyl,

(e) C_2-C_5-alkynyl,

where (a)-(e) are optionally substituted by

(1) OR^8, or

(2) halogen;

(f) C_6-C_{10}-aryl,

(g) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(h) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(i) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (f)-(i) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_nR^{10}$,

(5) NR^8R^9,

(6) OR^8, or

(7) $C(=O)R^{10}$,

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (f) – (i) are substituted by NR^8R^9,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl; and

wherein (a)-(c) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl, and

(c) C_3-C_6-cycloalkyl,

wherein (a)-(c) are optionally substituted by:

(1) halogen, or

(2) OR^{12},

wherein

R^{12} represents hydrogen or C_1-C_3-alkyl;

u is an integer from 0 - 2;

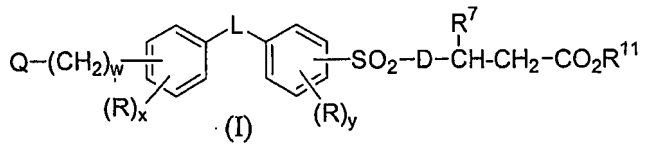
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

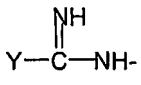
In another embodiment, the compounds of the invention are sulfones having the formula



(I)

in which D is CH_2 , L is a one-atom linker, and the various other groups and units are preferably defined as follows:

Q is a substituent selected from the group consisting of:

(a) 

wherein

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_3-C_5-alkenyl,

(a5) C_4-C_8-cycloalkenyl,

(a6) C_3-C_5-alkynyl,

(a7) C_6-C_{10}-aryl,

(a8) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(a9) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(a10) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and -NZ^1Z^2; and

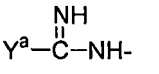
(a2) - (a10) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from

the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or $-NZ^1Z^2$, wherein

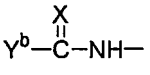
Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

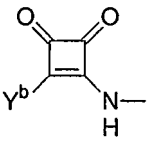
Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

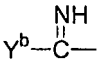
(b) 

wherein Y^a represents $-NH_2$ or -NH-Y;

(c) 

wherein X represents O or N(CN) ;

(d)  ;

(e) 

wherein for (c) - (e)

Y^b represents $-NH_2$, -NH-Y or -Y;

(f) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(f1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(f2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(f2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(f2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (f1) - (f2) are optionally substituted by R;

(g) Y^c=N-

wherein Y^c is as defined in (f) above;

(h) Y^dY^e-N-

wherein Y^d and Y^e are independently selected from the group consisting of hydrogen, C_1-C_5-alkyl, and C_1-C_5-aminoalkyl;

and

(i) when w = 0, Q forms a four to eight membered heterocyclic ring fused to the aryl group to which it is attached to form a bicyclic ring, wherein said heterocyclic ring contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and at least one carbon atom and said heterocyclic ring is optionally substituted with C_1-C_5-alkyl or -NZ^3Z^4 wherein Z^3 and Z^4 are

independently selected from the group consisting of hydrogen and C_1-C_5-alkyl;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1,

(g) $C(=O)OR^1$,

(h) $S(=O)_2OR^1$,

(i) NR^1R^2,

(j) $C(=O)NR^1R^2$, and

(k) $S(=O)_2NR^1R^2$;

wherein for (f)-(k):

R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

or

wherein for (i)-(k):

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) O,

(b) C(=O),

(c) CR^3R^4,

(d) $N(R^5)$,

(e) $S(=O)_z$, and

(f) $C(=NR^3)$

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_3-alkyl, and

(3) C_1-C_3-alkoxy;

wherein:

when an R^3 group is C_1-C_3-alkyl in L, said R^3 group may constitute a spiro or nonspiro ring wherein:

(a) the group R^3 is joined by a bond or by a heteroatom selected from the group consisting of oxygen, nitrogen and sulfur, to the carbon chain to which said group R^3 is attached, and taken together with the carbon chain atom(s) to which said group R^3 is attached, constitutes a ring of three to six members,

wherein for CR^3R^4, when R^3 is C_1-alkyl, the R^3 group is joined by a heteratom as defined above;

R^5 represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

D represents CH_2 ;

R^7 represents a substituent selected from the group consisting of:

(a) C_2-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_2-C_5-alkynyl,

where (a)-(f) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (g)-(j) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_2OH$,

(5) $S(=O)_nR^{10}$,

(6) $S(=O)_2NR^8R^9$,

(7) NR^8R^9,

(8) OR^8,

(9) $C(=O)R^{10}$,

(10) $C(=O)OR^8$; or

(11) $C(=O)NR^8R^9$;

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (g) – (j) are substituted by NR^8R^9, $S(=O)_2NR^8R^9$ or $C(=O)NR^8R^9$,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional

heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl;

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_3-C_5-alkynyl,

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (a)-(j) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl,

(c) C_3-C_6-cycloalkyl,

(d) C_3-C_6-alkenyl,

(e) C_5-C_6-cycloalkenyl, and

(f) C_3-C_6-alkynyl

wherein (b)-(f) are optionally substituted by:

(1) halogen,

(2) OR^{12}, or

(3) $NR^{12}R^{13}$;

wherein

R^{12} and R^{13} each independently represents hydrogen or C_1-C_3-alkyl;

or

R^{12} and R^{13} together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

u is an integer from 0 - 2;

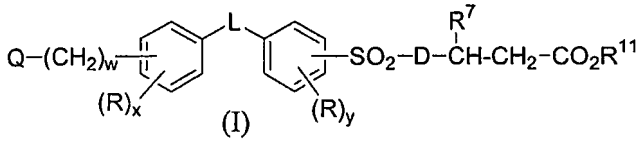
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

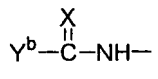
In another embodiment, the compounds of the invention are sulfones having the formula



(I)

in which D is CH_2 , L is a one-atom linker, and the various other groups and units are more preferably defined as follows:

Q is a substituent selected from the group consisting of:

(a) 

wherein

X represents O or N(CN) ;

Y^b represents $-NH_2$, -NH-Y or -Y; and

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_6-C_{10}-aryl,

(a5) C_6-C_{10}-aryl-C_1-C_3-alkyl, and

(a6) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and $-NZ^1Z^2$; and

(a2) - (a6) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or $-NZ^1Z^2$,

wherein

Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

(b) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(b1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(b2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which

contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(b2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(b2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (b1) - (b2) are optionally substituted by R;

(c) Y^c=N-

wherein Y^c is as defined in (b) above;

(d) Y^dY^e-N-

wherein Y^d and Y^e are independently selected from the group consisting of hydrogen, C_1-C_5-alkyl, and C_1-C_5-aminoalkyl;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1, and

(g) NR^1R^2,

wherein for (f)-(g):

R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

or

wherein for (i):

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) O,

(b) C(=O),

(c) CR^3R^4,

(d) $S(=O)_z$, and

(e) $C(=NR^3)$

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen, and

(2) C_1-C_3-alkoxy;

D represents CH_2 ;

R^7 represents a substituent selected from the group consisting of:

(a) C_2-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_2-C_5-alkynyl,

where (a)-(f) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (g)-(j) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_nR^{10}$,

(5) NR^8R^9,

(6) OR^8, or

(7) $C(=O)R^{10}$,

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (g) – (j) are substituted by NR^8R^9, ,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl;

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_3-C_5-alkynyl,

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (a)-(j) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl, and

(c) C_3-C_6-cycloalkyl,

wherein (a)-(c) are optionally substituted by:

(1) halogen,

(2) OR^{12}, or

(3) $NR^{12}R^{13}$;

wherein

R^{12} and R^{13} each independently represents hydrogen or C_1-C_3-alkyl;

or

R^{12} and R^{13} together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen

and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

u is an integer from 0 - 2;

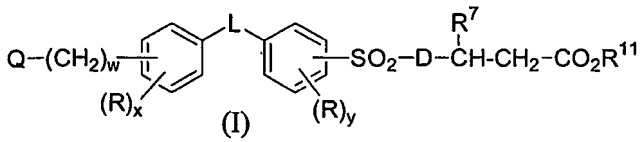
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

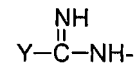
In another embodiment, the compounds of the invention are sulfones having the formula



(I)

in which D is CH_2 , L is a two-atom linker, and the various other groups and units are preferably defined as follows:

Q is a substituent selected from the group consisting of:

(a) 

wherein

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_3-C_5-alkenyl,

(a5) C_4-C_8-cycloalkenyl,

(a6) C_3-C_5-alkynyl,

(a7) C_6-C_{10}-aryl,

(a8) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(a9) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(a10) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which

contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

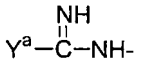
(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and $-NZ^1Z^2$; and

(a2) - (a10) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or $-NZ^1Z^2$, wherein

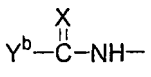
Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

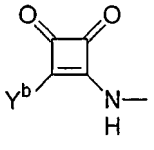
Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

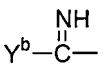
(b) 

wherein Y^a represents $-NH_2$ or -NH-Y;

(c) 

wherein X represents O or N(CN) ;

(d)  ;

(e) 

wherein for (c) - (e)

Y^b represents $-NH_2$, -NH-Y or -Y;

(f) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(f1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(f2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(f2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(f2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (f1) - (f2) are optionally substituted by R;

(g) Y^c=N-

wherein Y^c is as defined in (f) above;

(h) Y^dY^e-N-

wherein Y^d and Y^e are independently selected from the group consisting of hydrogen, C_1-C_5-alkyl, and C_1-C_5-aminoalkyl;
and

(i) when w = 0, Q forms a four to eight membered heterocyclic ring fused to the aryl group to which it is attached to form a bicyclic ring, wherein said heterocyclic ring contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and at least one carbon atom and said heterocyclic ring is optionally substituted with C_1-C_5-alkyl or $-NZ^3Z^4$ wherein Z^3 and Z^4 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl;

R represents a substituent selected from the group consisting of:

(a) halogen,
(b) C_1-C_4-alkyl, optionally substituted by halogen,
(c) C_6-C_{10}-aryl, optionally substituted by halogen,
(d) NO_2,
(e) CN,
(f) OR^1,
(g) $C(=O)OR^1$,
(h) $S(=O)_2OR^1$,
(i) NR^1R^2,
(j) $C(=O)NR^1R^2$, and
(k) $S(=O)_2NR^1R^2$;

wherein for (f)-(k):
R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,
(2) C_1-C_4-alkyl, optionally substituted by halogen, and
(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

or

wherein for (i)-(k):

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) $C(=O)N(R^5)$,

(b) $N(R^5)C(=O)$,

(c) $S(=O)_2N(R^5)$

(d) $N(R^5)S(=O)_2$,

(e) $CR^3R^4\text{-}CR^3R^4$,

(f) CH_2O,

(g) OCH_2,

(h) $CH_2N(R^5)$,

(i) $N(R^5)CH_2$,

(j) CH=CH, and

(k) $-C\equiv C-$;

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) C_1-C_3-alkyl, and

(4) C_1-C_3-alkoxy;

wherein:

when one or two R^3 groups are C_1-C_3-alkyl in L, said one or two R^3 groups may constitute spiro rings or nonspiro rings wherein:

(a) one group R^3 is joined by a bond or by a heteroatom selected from the group consisting of oxygen, nitrogen and sulfur, to the carbon chain to which said group R^3 is attached, and taken

together with the carbon chain atom(s) to which said group R^3 is attached, constitutes a ring of three to six members,

wherein for CR^3R^4, when R^3 is C_1-alkyl, the R^3 group is joined by a heteratom as defined above, or

(b) two groups R^3 are joined by a bond or by a heteroatom selected from the group consisting of oxygen, nitrogen and sulfur and taken together with the carbon chain atom(s) to which said two groups R^3 are attached, constitute a ring of 3-6 members;

R^5 represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

D represents CH_2 ;

R^7 represents a substituent selected from the group consisting of:

(a) C_2-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_2-C_5-alkynyl,

where (a)-(f) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms

selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (g)-(j) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,
(2) CN,
(3) halogen,
(4) $S(=O)_2OH$,
(5) $S(=O)_nR^{10}$,
(6) $S(=O)_2NR^8R^9$,
(7) NR^8R^9,
(8) OR^8,
(9) $C(=O)R^{10}$,
(10) $C(=O)OR^8$; or
(11) $C(=O)NR^8R^9$;

wherein:
R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (g) – (j) are substituted by NR^8R^9, $S(=O)_2NR^8R^9$ or $C(=O)NR^8R^9$,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,
(b) C_3-C_8-cycloalkyl,
(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl;
(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_3-C_5-alkynyl,

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (a)-(j) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl,

(c) C_3-C_6-cycloalkyl,

(d) C_3-C_6-alkenyl,

(e) C_5-C_6-cycloalkenyl, and

(f) C_3-C_6-alkynyl

wherein (b)-(f) are optionally substituted by:

(1) halogen,

(2) OR^{12}, or

(3) $NR^{12}R^{13}$;

wherein

R^{12} and R^{13} each independently represents hydrogen or C_1-C_3-alkyl;

or

R^{12} and R^{13} together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

u is an integer from 0 - 2;

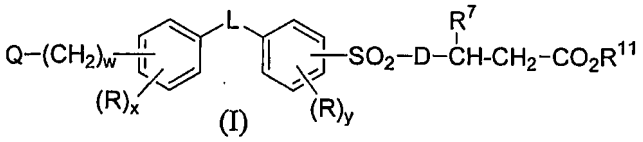
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

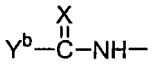
In another embodiment, the compounds of the invention are sulfones having the formula



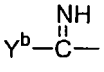
(I)

in which D is CH_2 , L is a two-atom linker, and the various other groups and units are more preferably defined as follows:

Q is a substituent selected from the group consisting of:

(a) 

wherein X represents O or N(CN) ;

(b) 

wherein for (a) and (b),

Y^b represents $-NH_2$, -NH-Y or -Y; and

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_6-C_{10}-aryl,

(a5) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(a6) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(a7) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which

contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and $-NZ^1Z^2$; and

(a2) - (a7) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or $-NZ^1Z^2$,

wherein

Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

(c) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(c1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(c2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered

saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(c2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(c2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (c1) - (c2) are optionally substituted by R;

(d) Y^c=N-

wherein Y^c is as defined in (c) above;

(e) Y^dY^e-N-

wherein Y^d and Y^e are independently selected from the group consisting of hydrogen, C_1-C_5-alkyl, and C_1-C_5-aminoalkyl;

and

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1, and

(g) NR^1R^2,

wherein for (f)-(g):

R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

or

wherein for (g):

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) CR^3R^4-CR^3R^4,

(b) CH_2O,

(c) OCH_2,

(d) $CH_2N(R^5)$,

(e) $N(R^5)CH_2$,

(f) CH=CH, and

(g) -C≡C- ;

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) halogen, and

(3) C_1-C_3-alkoxy;

R^5 represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

D represents CH_2 ;

R^7 represents a substituent selected from the group consisting of:

(a) C_2-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_2-C_5-alkynyl,

where (a)-(f) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (g)-(j) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_nR^{10}$,

(5) NR^8R^9,

(6) OR^8, and

(7) $C(=O)R^{10}$,

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (g) – (j) are substituted by NR^8R^9,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl;

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl;

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_3-C_5-alkynyl,

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (a)-(j) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl, and

(c) C_3-C_6-cycloalkyl,

wherein (b)-(c) are optionally substituted by:

(1) halogen,

(2) OR^{12}, or

(3) $NR^{12}R^{13}$;

wherein

R^{12} and R^{13} each independently represents hydrogen or C_1-C_3-alkyl;

or

R^{12} and R^{13} together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

u is an integer from 0 - 2;
v is an integer from 1 - 2;
n, w and z are each independently an integer from 0 - 2;
a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

The compounds of the present invention may contain asymmetric centers, depending upon the nature of the various substituents. Each such asymmetric center will produce two optical isomers. Multiple asymmetric centers in a compound will also produce diastereomers. In certain instances, asymmetry may also be present due to restricted rotation about a central bond joining the two aromatic rings of the specified compounds. It is intended that all isomers, either by nature of asymmetric centers or by restricted rotation as described above, as separated, pure or partially purified isomers or racemic mixtures thereof, be included within the scope of the invention.

In cases in which the compounds have unsaturated carbon-carbon or carbon-nitrogen double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention.

In cases where the compounds may exist in tautomeric forms, each tautomeric form is contemplated as being encompassed by the scope of the invention whether existing in equilibrium with its corresponding tautomeric form or forms, or whether set in that form through chemical derivatization.

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

Salts are especially the pharmaceutically acceptable salts of compounds of formulae (I) or (II) such as, for example, organic or inorganic acid addition salts of compounds of formulae (I) or (II). Suitable inorganic acids include but are not limited to halogen acids (such as hydrochloric acid), sulfuric acid, or phosphoric acid. Suitable organic acids include but are not limited to carboxylic, phosphonic, sulfonic, or sulfamic acids, with examples including acetic acid, trifluoroacetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2- or 3-hydroxybutyric acid, γ-aminobutyric acid (GABA), gluconic acid, glucosemonocarboxylic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, para-toluenesulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, fumaric acid, oxalic acid, succinic acid, adipic acid, pimelic acid, suberic acid, azeiaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids (such as glutamic acid, aspartic acid, N-methylglycine, acetytaminoacetic acid, N-acetylasparagine or N-acetylcysteine), pyruvic acid, acetoacetic acid, phosphoserine, and 2- or 3-glycerophosphoric acid.

In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2}, Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Prodrugs are considered to be any covalently bonded carriers which release the active parent compound of formula (I) or (II) *in vivo*. Formation of prodrugs is well known in the art in order to enhance the properties of the parent compound; such properties include solubility, absorption, biostability and release time (see *"Pharmaceutical Dosage Form and Drug*

Delivery Systems" (Sixth Edition), edited by Ansel et al., publ. by Williams & Wilkins, pgs. 27-29, (1995) which is hereby incorporated by reference).

Commonly used prodrugs of the disclosed compounds of formulae (I) and (II) are designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Tenth Edition), editor Hardman et al., publ. by McGraw-Hill, pages 12-18, (2001), which is hereby incorporated by reference).

Definition of Terms

The term "halogen" or "halo" includes fluorine, chlorine, bromine, and iodine substituents for the purposes of this invention. When halogen is a possible substituent on an alkyl group, the alkyl may be fully substituted, up to perhalo.

When "L" is a two-atom linker, it is to be understood that the left-most moiety of each of the "L" variants is connected to the ring drawn on the left of the group "L" in the general formulae, and that the right-most moiety of the linker is connected to the ring drawn on the right of the group "L" in the general formulae. For example, the use of the linker "-O-CH_2-" is depicted by Figure (1) and of the linker "-CH_2-O-" is depicted by Figure (2) below:

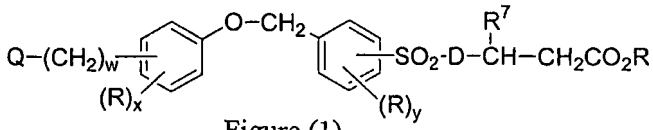


Figure (1)

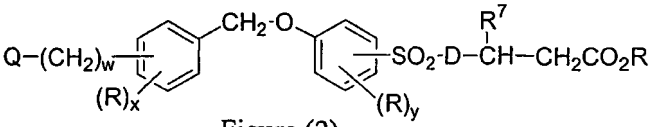


Figure (2)

The term "fused bicyclic ring" as it appears in the specification and claims refers to a substituent which is a two ring structure which share two atoms (e.g. two carbons; one nitrogen and one carbon atom; or two nitrogen atoms). The bonding between the fused

bicyclic ring and the compound and/or atom to which it is attached can be through either of the two rings.

Description of the Compositions

The invention also includes pharmaceutical compositions comprising one or more of the compounds of formulae (I) and (II), purified stereoisomers or stereoisomer mixtures, or their salt or prodrug forms thereof or their salts or prodrugs forms thereof, with a pharmaceutically acceptable ingredient.

The invention also relates to pharmaceutical compositions containing compounds of formulae (I) and (II), purified stereoisomers or stereoisomer mixtures, or their salt or prodrug forms thereof and their use in combination with other drugs or therapies for the treatment of diseases and/or conditions associated with the $\alpha_v\beta_3$ integrin and/or $\alpha_v\beta_5$ integrin.

The pharmaceutical compositions are prepared so that they may be administered orally, dermally, parenterally, nasally, ophthalmically, otically, sublingually, rectally or vaginally. Dermal administration includes topical application or transdermal administration. Parenteral administration includes intravenous, intraarticular, intramuscular, and subcutaneous injections, as well as use of infusion techniques. One or more compounds of the invention may be present in association with one or more non-toxic pharmaceutically acceptable ingredients and optionally, other active anti-proliferative agents, to form the pharmaceutical composition. These compositions can be prepared by applying known techniques in the art such as those taught in *Remington's Pharmaceutical Sciences* (Fourteenth Edition), Managing Editor, John E. Hoover, Mack Publishing Co., (1970) or *Pharmaceutical Dosage Form and Drug Delivery Systems* (Sixth Edition), edited by Ansel et al., publ. by Williams & Wilkins, (1995), each of which is hereby incorporated by reference.

Commonly used pharmaceutical ingredients which can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, F_2ClC-$CClF_2$ and $CClF_3$)

air displacement agents (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers);

buffering agents (examples include but are not limited to potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate);

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerin, propylene glycol and sorbitol);

levigating agents (examples include but are not limited to mineral oil and glycerin);

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerin);

solvents (examples include but are not limited to alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate);

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch);

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate; kaolin, lactose, mannitol, microcrystalline cellulose, powedered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to carnuba wax and white wax);

thickening agents (examples include but are not limited to beewax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, polyoxyethylene stearate,).

Depending on the route of administration, the compositions can take the form of aerosols, capsules, creams, elixirs, emulsions, foams, gels, granules, inhalants, lotions, magmas,

ointments, peroral solids, powders, sprays, syrups, suppositories, suspensions, tablets and tinctures.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions containing the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as

polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl, *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The compounds may also be administered in the form of suppositories for rectal or vaginal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal or vaginal temperature and will therefore melt in the rectum or vagina to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compounds of the invention may also be administered transdermally using methods known to those skilled in the art (see, for example: Chien; "Transdermal Controlled Systemic Medications"; Marcel Dekker, Inc.; 1987. Lipp et al. WO 94/04157 3Mar94). For example, a solution or suspension of a compound of formula I in a suitable volatile solvent optionally containing penetration enhancing agents can be combined with additional additives known to those skilled in the art, such as matrix materials and bacteriocides. After sterilization, the resulting mixture can be formulated following known procedures into dosage forms. In addition, on treatment with emulsifying agents and water, a solution or suspension of a compound of formula I may be formulated into a lotion or salve.

Suitable solvents for processing transdermal delivery systems are known to those skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol, lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate, polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane or benzene, or halogenated hydrocarbons such as dichloromethane, chloroform, trichlorotrifluoroethane, or trichlorofluoroethane. Suitable solvents may also include mixtures one or more materials selected from lower alcohols, lower ketones , lower carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

Suitable penetration enhancing materials for transdermal delivery systems are known to those skilled in the art, and include, for example, monohydroxy or polyhydroxy alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated C_8-C_{18} fatty alcohols such as lauryl alcohol or cetyl alcohol, saturated or unsaturated C_8-C_{18} fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to 24 carbons such as methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl isobutyl *tert*-butyl or monoglycerin esters of acetic acid, capronic acid, lauric acid, myristinic acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate, diisopropyl sebacate, diisopropyl maleate, or

diisopropyl fumarate. Additional penetration enhancing materials include phosphatidyl derivatives such as lecithin or cephalin, terpenes, amides, ketones, ureas and their derivatives, and ethers such as dimethyl isosorbid and diethyleneglycol monoethyl ether. Suitable penetration enhancing formulations may also include mixtures one or more materials selected from monohydroxy or polyhydroxy alcohols, saturated or unsaturated C_8-C_{18} fatty alcohols, saturated or unsaturated C_8-C_{18} fatty acids, saturated or unsaturated fatty esters with up to 24 carbons, diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons, phosphatidyl derivatives, terpenes, amides, ketones, ureas and their derivatives, and ethers.

Suitable binding materials for transdermal delivery systems are known to those skilled in the art and include polyacrylates, silicones, polyurethanes, block polymers, styrene-butadiene coploymers, and natural and synthetic rubbers. Cellulose ethers, derivatized polyethylenes, and silicates may also be used as matrix components. Additional additives, such as viscous resins or oils may be added to increase the viscosity of the matrix.

Optional anti-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the Merck Index, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowldeged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Tenth Edition), editor Hardman et al., publ. by McGraw-Hill, pages 1389-1459, (2001), which is hereby incorporated by reference, such as aminoglutethimide, anastrazole, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, camptothecin, diethylstilbestrol, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, exemestane, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate,

fluoxymesterone, flutamide, formestane, hydroxyprogesterone caproate, gemcitabine, idarubicin, IL-2, α-interferon, letrozole, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, oxaliplatin, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, temozolomide, trimethylmelamine, uridine, vinorelbine and vorozole.

Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone.

Optional agents for the treatment of osteoporosis suitable for use with the composition of the invention include but are not limited to those compounds acknowldeged to be used in the treatment of osteoporosis in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Tenth Edition), ed. Hardman et al., publ. by McGraw-Hill, pages 1736-1739, (2001), which is hereby incorporated by reference, which includes:

(a) calcium-based anti-resorptive agents which include but are not limited to calcium carbonate, calcium citrate, calcium gluconate, calcium lactate, calcium phosphate and hydroxyapatite ($Ca_5(OH)(PO_4)_3$);

(b) vitamin D and its analogs which include but are not limited to calcitrio and 1α-hydroxycholecalciferol;

(c) estrogen-based compounds which include but are not limited to estrogen, conjugated equine estrogens and medroxyprogesterone acetate;

(d) selective estradiol receptor modulators which include but are not limited to raloxifene;

(e) bisphosphonate-based compounds which include but are not limited to alendronate, pamidronate and risendronate;

(f) thiazide diuretic compounds which include but are not limited to hydrochlorothiazide;

(g) calcitonin; and

(h) nandrolone decanoate.

For all regimens of use disclosed herein for compounds of formulae (I) or (II), the daily oral dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to

200 mg/kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of formulae (I) or (II) or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

Description of Preparative Methods

EXAMPLES

All reactions were performed in dry glassware under a positive pressure of dry argon, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Unless otherwise stated, the term 'concentration under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mmHg. Unless otherwise stated, the term 'under high vacuum' refers to a vacuum of 0.4 – 1.0 mmHg.

All temperatures are reported uncorrected in degrees Celsius (°C). Unless otherwise indicated, all parts and percentages are by weight.

Commercial grade reagents and solvents were used without further purification.

Thin-layer chromatography (TLC) was performed using Whatman® pre-coated glass-backed silica gel 60A F-254 250 μm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, (d) immersion of the plate in a cerium sulfate solution followed by heating, and/or (e) immersion of the plate in an acidic ethanol solution of 2,4-dinitrophenylhydrazine followed by heating.

Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel.

Melting points (mp) were determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected. Fourier transform infrared sprectra were obtained using a Mattson 4020 Galaxy Series spectrophotometer. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me_4Si (δ 0.00) or residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (^{13}C)

NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent ($CDCl_3$ δ 77.0; MeOD-d_3; δ 49.0; DMSO-d_6 δ 39.5) as standard. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were either obtained as electron impact (EI) mass spectra or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (EI-MS) were obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Vacumetrics Desorption Chemical Ionization Probe for sample introduction. The ion source was maintained at 250 °C. Electron impact ionization was performed with electron energy of 70 eV and a trap current of 300 μA. Liquid-cesium secondary ion mass spectra (FAB-MS), an updated version of fast atom bombardment were obtained using a Kratos Concept 1-H spectrometer. Chemical ionization mass spectra (CI-MS) were obtained using a Hewlett Packard MS-Engine (5989A) with methane or ammonia as the reagent gas ($1x10^{-4}$ torr to $2.5x10^{-4}$ torr). The direct insertion desorption chemical ionization (DCI) probe (Vaccumetrics, Inc.) was ramped from 0-1.5 amps in 10 sec and held at 10 amps until all traces of the sample disappeared (~1-2 min). Spectra were scanned from 50-800 amu at 2 sec per scan. HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a C-18 column, and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-800 amu using a variable ion time according to the number of ions in the source. Gas chromatography - ion selective mass spectra (GC-MS) were obtained with a Hewlett Packard 5890 gas chromatograph equipped with an HP-1 methyl silicone column (0.33 mM coating; 25 m x 0.2 mm) and a Hewlett Packard 5971 Mass Selective Detector (ionization energy 70 eV). Elemental analyses are conducted by Robertson Microlit Labs, Madison NJ.

All compounds displayed NMR spectra, LRMS and either elemental analysis or HRMS consistant with assigned structures.

List of Abbreviations and Acronyms:

AcOH	acetic acid
anh	anhydrous
9-BBN	9-borabicyclo[3.3.1]nonane
BOC	*tert*-butoxycarbonyl

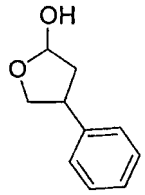
conc	concentrated
dec	decomposition
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether
Et_3N	triethylamine
mCPBA	*meta*-chloroperoxybenzoic Acid
MeOH	methanol
THF	tetrahydrofuran
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl

A. General Methods for Synthesis of Phenylsulfonyl Precursors

A1. General Method for Synthesis of Methyl 4-[(4-Hydroxyphenyl)sulfonyl]-3-arylbutanoate Analogues via Lactone opening:

A1a Methyl 4-[(4-Bromophenyl)sulfonyl]-3-phenylbutanoate

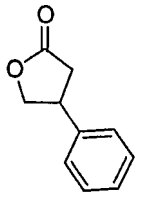
A1a Step 1



To a mixture of iodobenzene (200 g, 1 mol), (2*Z*)but-2-ene-1,4-diol (259 g, 3 mol, 3 equiv), Bu_4NCl (316 g, 0.98 mol, 1 equiv) and K_2CO_3 (406 g, 3 mol, 3 equiv) in anh. DMF (3 L) was added $Pd(OAc)_2$ (22 g, 0.1 mol, 0.1 equiv). The reaction mixture was heated at 90 °C overnight and allowed to cool to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (2 L), washed with water (4x500 mL), a saturated NaCl solution (500 mL),), dried (Na_2SO_4) and concentrated under

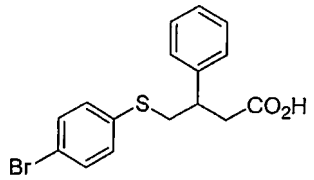
reduced pressure. The crude product was purified by flash chromatography (gradient from 5% to 20% EtOAc/hex) to afford crude 4-phenyloxolan-2-ol (98 g) as an orange oil: TLC (25% EtOAc/hex) R_f 0.36; LCMS ES-MS *m/z* 165 (MH^+). This product was taken to the next step without further purification.

A1a Step 2



To a 0 °C solution of crude 4-phenyloxolan-2-ol (5, 598 g) in CH_2Cl_2 (500 mL) was added Florisil®, followed by PCC (190 g, 0.9 mol). The reaction mixture was stirred for 10 min, then was allowed to warm to room temperature. The resulting mixture was concentrated under reduced pressure and filtered through a pad of Celite® with the aid of EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (gradient from hex to 15% EtOAc/hex). The resulting oil was mixed with hexane and concentrated under reduced pressure to give 3-phenyl-butyrolactone (75 g, 46% for 2 steps) as a yellow solid: TLC (20% EtOAc/hex) R_f 0.46; ^1H NMR ($CDCl_3$) δ 2.68 (dd, *J*=9.1, 17.3 Hz, 1H), 2.94 (dd, *J*=8.6, 17.4 Hz, 1H), 3.74-3.85 (m,, 1H), 4.28 (app t, *J*=8.5 Hz, 1H), 4.68 (app t, *J*=8.3H, 1H), 7.22-7.40 (m, 5H).

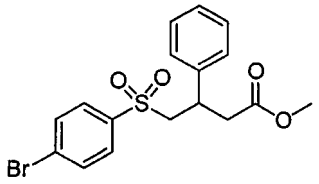
A1a Step 3



To a mixture of NaH (1.3 g, 54 mmol, 1.1 equiv) in DMF (100 mL) was added dropwise a solution of 4-bromothiophenol (9.26 g, 49 mmol, 1.0 equiv) in DMF (20 mL) and the resulting mixture was stirred for 10 min. 3-Phenyl-butyrolactone (8.0 g, 50 mmol) was then added and the reaction mixture was heated at 70 °C overnight, cooled to room temperature and treated with a 1N HCl solution (100 mL). The resulting mixture was extracted with EtOAc, washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The

crude product was purified by flash chromatography (gradient from hexane to 50% EtOAc/hex to EtOAc) to give 4-(4-bromophenylthio)-3-phenylbutanoic acid (12 g) as a slightly impure light yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.70 (dd, *J*=8.3, 16.2 Hz, 1H), 2.99 (dd, *J*=6.1, 16.2 Hz, 1H), 3.17 (d, *J*=7.5 Hz, 2H), 3.28-3.38 (m, 1H), 7.15-7.46 (m, 9H), 10.13 (br s, 1H).

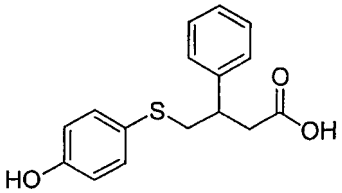
A1a Step 4



To a solution of 4-(4-bromophenylthio)-3-phenylbutanoic acid (12 g, 34 mmol) in MeOH (175 mL) was added conc H_2SO_4 (0.2 mL). The reaction mixture was heated at 75 °C overnight and at 80 °C for 5 h. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with a saturated $NaHCO_3$ solution and water, dried ($MgSO_4$) and concentrated under reduced pressure to give 10.6 g of a yellow oil. The crude oil was dissolved in CH_2Cl_2 (150 mL) and treated with a solution of *m*CPBA (17.8 g, 103 mmol, 3.0 equiv) in CH_2Cl_2 (100 mL). The reaction mixture was stirred at room temperature overnight and washed with a 1N NaOH solution. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield methyl 4-[(4-bromophenyl)sulfonyl]-3-phenylbutanoate (5.3 g, 27% for 3 steps) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.72 (dd, *J*=8.0, 16.1 Hz, 1H), 2.96 (dd, *J*=6.0, 16.1 Hz, 1H), 3.47 (dd, *J*=6.9, 14.2 Hz, 1H), 3.57-3.82 (m, 6H), 7.04-7.07 (m, 2H), 7.19-7.21 (m, 3H), 7.58 (s, 5H); HPLC ES-MS *m/z* 398 ($(M+1)^+$).

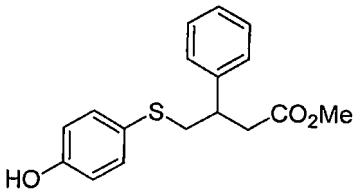
A1b: Methyl 4-[(4-Hydroxyphenyl)sulfonyl]-3-phenylbutanoate

A1b Step 1



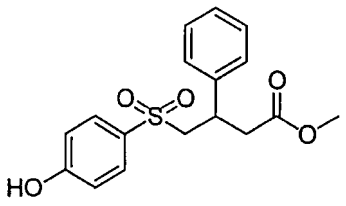
To a 0 ^{0}C solution of 4-hydroxythiophenol (17.1 g, 136 mmol, 1.1 equiv.) in anh. DMF (200 mL) was added NaH (3.6 g, 148 mmol, 1.2 equiv.) in small portions. The resulting mixture was stirred for 40 min. at room temperature, treated with 2-phenylbutyrolactone (20.0 g, 123 mmol) and heated to 80 ^{0}C for 2 days. The mixture was then concentrated under reduced pressure. The residue was taken up in EtOAc (200 mL) and was extracted with a 1 N NaOH solution (2x100 mL). The organic layers were combined, washed with a saturated NaCl solution (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (11 cm x 10 cm SiO_2, gradient from 30% EtOAc/hexanes to 0.5% AcOH/EtOAc) to afford 4-(4-hydroxyphenylthio)-3-phenylbutanoic acid (32.9 g, 92%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.67 (dd, J_1 = 8.5 Hz, J_2 = 15.8 Hz, 1H), 3.00-3.29 (m, 4H), 6.75 (d, J = 6.6 Hz, 2H), 7.15-7.33 (m, 7H), 7.50-9.55 (br s, 2H).

A1b Step 2



A solution of 4-(4-hydroxyphenylthio)-3-phenylbutanoic acid (32.9 g, 114 mmol) in a mixture of MeOH (500 mL) and conc. H_2SO_4 (3 mL) was heated at the reflux temperature for 20 h. The mixture was concentrated under reduced pressure. The residue was taken up in EtOAc (500 mL) and washed with a saturated aqueous $NaHCO_3$ solution. The organic layer was concentrated under reduced pressure, treated with CH_2Cl_2 and concentrated under reduced pressure again. The crude product was filtered through a plug of silica gel to afford methyl 4-(4-hydroxyphenylthio)-3-phenylbutanoate (27.3 g, 79%) as a yellow oil: TLC (20% EtOAc/hexanes) R_f 0.28; ^{1}H NMR ($CDCl_3$) δ 2.68 (dd, J_1 = 8.8 Hz, J_2 = 15.4 Hz, 1H), 3.02-3.17 (m, 3H), 3.27-3.35 (m, 1H), 3.60 (s, 3H), 5.95 (s, 1H), 6.77 (d, J = 7.0 Hz, 2H), 7.16-7.33 (m, 7H); ES-LCMS *m/z* (rel abundance) 303 (MH^+, 75%).

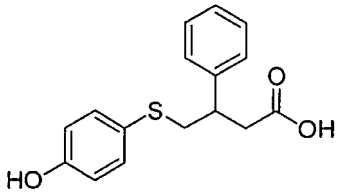
A1b Step 3



A solution of methyl 4-(4-hydroxyphenylthio)-3-phenylbutanoate (27.2 g, 90 mmol) in acetone (500 mL) was placed in water bath and treated with a slurry of Oxone® (136 g, 221 mmol, 2.5 equiv.) in water (250 mL). The resulting mixture was stirred for 2 h. The mixture was concentrated nearly to dryness under reduced pressure and the residue was taken up into EtOAc (500 mL). The organic layer was washed with a saturated NaCl solution (200 mL), dried (Na_2SO_4), concentrated under reduced pressure, treated with CH_2Cl_2/hexanes (1:1) and concentrated under reduced pressure again to afford methyl 4-[(4-hydroxyphenyl)sulfonyl]-3-phenylbutanoate (28.2 g, 94%) as a white solid: TLC (30% EtOAc/hexanes) R_f 0.17; ^{1}H NMR ($CDCl_3$) δ 2.75 (dd, J_1 = 8.8 Hz, J_2 = 15.8 Hz, 1H), 3.05 (dd, J_1 = 5.5 Hz, J_2 = 15.8 Hz, 1H), 3.40-3.73 (m, 6H), 6.85 (d, J = 7.3 Hz, 2H), 7.07 (d, J = 7.3 Hz, 2H), 7.15-7.28 (m, 4H), 7.63 (d, J = 8.8 Hz, 2H); HPLC ES-MS *m/z* (rel abundance) 335 ($(M+1)^+$, 100%).

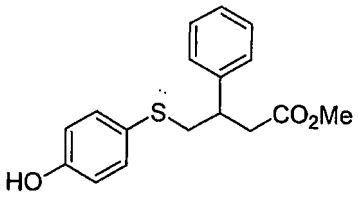
A1c: Methyl 4-[(4-hydroxyphenyl)sulfonyl]-3-phenylbutanoate

A1c Step 1



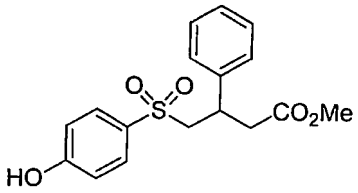
To a mixture of NaH (178 mg, 7.4 mmol, 1.2 equiv) in anh. DMF (20 mL) was added 4-hydroxythiophenol (0.78 g, 6.2 mmol), followed by 3-phenyl-butyrolactone (1.0 g, 6.2 mmol, 1 equiv). The reaction mixture was stirred at room temperature overnight and heated at 80 °C for 26 h. The resulting mixture was diluted with EtOAc (100 mL) and extracted with a 1N NaOH solution (100 mL). The aqueous layer was adjusted to pH 1 using a conc. HCl solution and extracted with EtOAc (2x200 mL). The combined organic layers were washed with a saturated NaCl solution (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give 4-(4-hydroxyphenylthio)-3-phenylbutanoic acid (1.84 g) as a yellow oil. TLC (30% EtOAc/hex) R_f0.16. The crude product was used without further purification.

A1c Step 2



To a solution of crude 4-(4-hydroxyphenylthio)-3-phenylbutanoic acid (38 g) in EtOH (100 mL) was added conc. H_2SO_4 (5 mL). The reaction mixture was heated at the reflux temperature for 2 d, then concentrated under reduced pressure. The residue was dissolved in EtOAc (500 mL), washed with a saturated $NaHCO_3$ solution (2x500 mL) and a saturated NaCl solution (300 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give methyl 4-(4-hydroxyphenylthio)-3-phenylbutanoate (23.4 g) as an orange oil. The crude product was used without further purification.

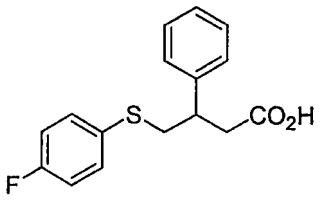
A1c Step 3



To a 0 °C solution of ethyl 4-(4-hydroxyphenylthio)-3-phenylbutanoate (23.3 g) in acetone (500 mL) was added a slurry of Oxone® (142 g, 231 mmol) in water (250 mL). The reaction mixture was stirred at room temperature for 3 d. The resulting mixture was filtered, the filtrate was concentrated to about 300 mL and extracted with EtOAc (500 mL). The organic layer was washed with a saturated NaCl solution (200 mL) and filtered through a pad of silica gel with the aid of EtOAc. The filtate was concentrated and the residue was purified by flash chromatography (10% EtOAc/hex) to give Methyl 4-[(4-hydroxyphenyl)sulfonyl]-3-phenylbutanoate (16.7 g, 37% for 3 steps) as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.74 (dd, *J*=8.7, 15.9 Hz, 1H), 3.03 (dd, *J*=5.5, 16.1 Hz, 1H), 3.42 (dd, *J*=6.0, 14.2 Hz, 1H), 3.49-3.59 (m, 4H), 3.64-3.74 (m, 1H), 6.80-6.85 (m, 2H), 7.03-7.07 (m, 2H), 7.13-7.28 (m, 3H), 7.34 (s, 1H), 7.58-7.65 (m, 2H).

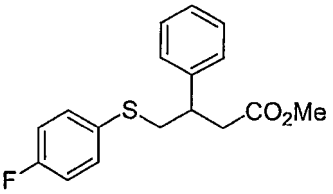
A1d: Methyl 4-[(4-Fluorophenyl)sulfonyl]-3-phenylbutanoate

A1d Step 1



A 0 °C solution of 4-fluorobenzenethiol (11.8 g, 92.5 mmol, 1.5 equiv) in. DMF (100 mL) was treated with NaH (3.0 g, 123.3 mmol, 2.0 equiv), stirred for 30 min, then treated with 2-phenylbutyrolactone (10.0 g, 61.7 mmol). The reaction mixture was heated to 100 °C for 17 h, then let it cool to room temperature. The solvent was evaporated under reduced pressure. The residue was taken up into EtOAc (200 mL), and washed with 1N aqueous HCl solution (200 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The cude mixture was purified by flash chromatography (11 cm x 13 cm SiO_2, gradient from 20% EtOAc/hexanes to 1% AcOH/EtOAc) to afford 4-[(4-fluorophenyl)thio]-3-phenylbutanoic acid (15.4 g, 86%) as a brown oil; ^1H NMR ($CDCl_3$) δ 2.70 (dd, J_1 = 7.7 Hz, J_2 = 15.8 Hz, 1H), 3.01-3.34 (m, 4H), 6.97-7.03 (m, 2H), 7.17-7.40 (m, 7H), 11.0-11.7 (br s, 1H); GC-MS *m/z* (rel abundance) 290 (M^+, 61%).

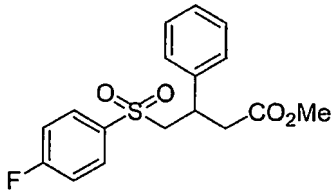
A1d Step 2



A solution of 4-[(4-fluorophenyl)thio]-3-phenylbutanoic acid (15.4 g, 53 mmol) in MeOH (100 mL) was treated with 1 mL conc H_2SO_4 and was heated at the reflux temperature for 22 h. The reaction mixture was concentrated under reduced pressure. The residue was taken up into EtOAc (200 mL) and was washed with saturated aqueous sodium bicarbonate solution (2x200 mL) and saturated sodium chloride solution (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (11 cm x 11 cm SiO_2, 5% EtOAc/hexanes) to afford methyl 4-[(4-

fluorophenyl)thio]-3-phenylbutanoate (10.4 g, 63%) as a yellow oil; TLC (10% EtOAc/hexanes) R_f 0.49; ^{1}H NMR ($CDCl_3$) δ 2.68 (dd, J_1 = 8.5 Hz, J_2 = 15.8 Hz, 1H), 2.97 (dd, J_1 = 6.6 Hz, J_2 = 15.8 Hz, 1H), 3.17 (d, J = 7.9 Hz, 2H), 3.30-3.40 (m, 1H), 3.59 (s, 3H), 6.97-7.03 (m, 2H), 7.17-7.36 (m, 7H).

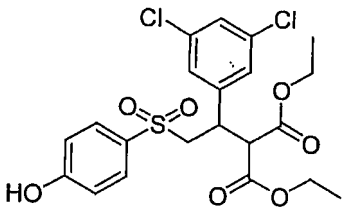
A1d Step 3



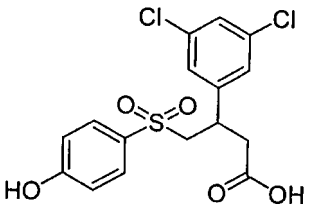
To a 0 °C solution of methyl 4-[(4-fluorophenyl)thio]-3-phenylbutanoate (5.2 g, 17.1 mmol) in $CHCl_3$ (100 mL) was added mCPBA (14.7 g, 77%, 65.6 mmol, 3.8 equiv). The resulting white slurry was allowed to warm to room temperature and was stirred for 17 h followed by the addition of Na_2SO_3 (14.0 g, 111 mmol, 6.5 equiv) to quench the excess mCPBA. The reaction was stirred for 20 min, then washed with saturated aqueous sodium bicarbonate solution (100 mL). The layers were separated, the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (100 g SiO_2, gradient from 5% EtOAc/hexanes to 20% EtOAc/20% CH_2Cl_2/hexanes) to afford methyl 4-[(4-fluorophenyl)sulfonyl]-3-phenylbutanoate (5.2 g, 91%) as a white solid; TLC (20% EtOAc/hexanes) R_f 0.22; ^{1}H NMR ($CDCl_3$) δ 2.73 (dd, J_1 = 8.1 Hz, J_2 = 15.8 Hz, 1H), 2.97 (dd, J_1 = 5.5 Hz, J_2 = 15.8 Hz, 1H), 3.44-3.76 (m, 6H), 7.05-7.27 (m, 7H), 7.74-7.78 (m, 2H); GCMS *m/z* (rel abundance) 337 (MH^+, 3%).

A2. Synthesis of Methyl 4-[(4-Hydroxyphenyl)sulfonyl]-3-arylbutanoate Analogues via Michael Addition to Vinylidene Malonate: Diethyl 2-{1-(3,5-Dichlorophenyl)-2-[(4-hydroxyphenyl)sulfonyl]ethyl}malonate

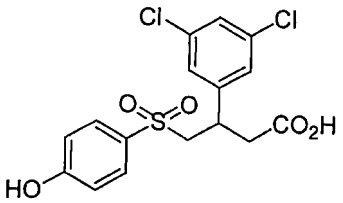
A2 Step 1



To a solution of 4-methylsulphonylphenol (3.3 g, 19 mmol) in anh. THF (120 mL) was added *n*-BuLi (19 mL, 2.0 M in pentane) dropwise at -78 °C. After stirring for 2 h, the yellow slurry was transferred via syringe to a solution of diethyl (3,5-dichlorobenzylidene)malonate (5.9 g, 18.6 mmol) in THF (20 mL) at -78 °C. The resulting clear solution was stirred for 2 hrs, then partitioned between EtOAc (300 mL) and a 1 M HCl solution (130 mL). The organic phase was washed with a saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under reduced pressure to afford diethyl 2-{1-(3,5-dichlorophenyl)-2-[(4-hydroxyphenyl)sulfonyl]ethyl}malonate as a white solid (5.8 g, 64% yield): R_f (EtOAc-hexane, 4:6) 0.36; ^1H NMR (DMSO-d_6): 0.85 (t, 3H), 1.15 (t, 3H), 3.35 (s, 1H), 3.48 (dd, 1H), 3.6(t, 1H), 3.85 (q, 2H), 3.92 (d, 1H), 4.00 (d, 1H), 4.15 (q, 2H), 6.78 (d, 2H), 7.20 (s, 2H), 7.35 (s, 1H), 7.40 (d, 2H).



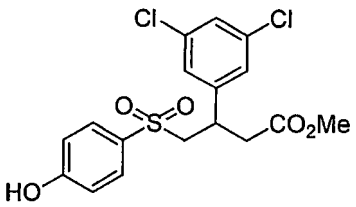
A2 Step 2



A solution of diethyl 2-{1-(3,5-dichlorophenyl)-2-[(4-hydroxyphenyl)-sulfonyl]-ethyl}malonate (0.5 g,1.0 mmol) and 0.25 g of KOH (4.0 mmol) in a mixture of 50 mL of MeOH and 1.5 mL of water was stirred at room temperature for 2 hrs. The solution was acidified with a 1.0 M HCl solution, then extracted with EtOAc. The organic phase was

dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in CH_3CN (20 mL), treated with Cu_2O (0.030 g, 0.08 mmol) and heated at the reflux temperature for 2.5 hrs. The mixture was then concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2; gradient from 30% EtOAc/hexane to 50% EtOAc/hexane, then with 100% EtOAc, and then to 10% MeOH/CH_2Cl_2) to give 3-(3,5-dichlorophenyl)-4-[(4-hydroxyphenyl)sulfonyl]butanoic acid (0.14 g, 24%): R_f (10% MeOH/CH_2Cl_2) 0.36.

A2 Step 3

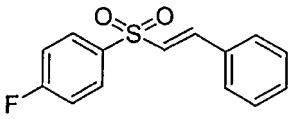


A solution of 0.14 g of 3-(3,5-dichlorophenyl)-4-[(4-hydroxyphenyl)sulfonyl]butanoic acid (0.14 g, 0.36 mmol) in MeOH that had been treated with 3 drops of H_2SO_4 was heated at the reflux temperature for 4 h. The mixture was then concentrated, and the residue was dissolved in EtOAc. The organic solution was washed with water twice, dried ($MgSO_4$) and concentrated under reduced pressure to afford methyl 3-(3,5-dichlorophenyl)-4-[(4-hydroxyphenyl)sulfonyl]butanoate as an oil (0.137 g, 94%): R_f (50% EtOAc/hexane) 0.58.

A3. Synthesis of Methyl 4-[(4-Hydroxyphenyl)sulfonyl]-3-arylbutanoate Analogues via Addition to Vinylsulfone

A3a: 4-[(4-Fluorophenyl)sulfonyl]-3-phenylbutanoic Acid

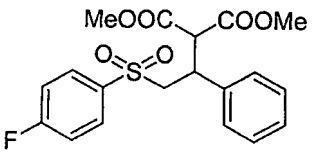
A3a Step 1



A solution of 4-fluorophenylsulfonyl chloride (609 g, 3.13 moles), styrene (486 g, 4.67 moles) and copper(II) chloride (20.95 g, 156 mmol) in CH_3CN (4 L) was heated under a gentle reflux under argon. An exotherm occurred upon reaching the reflux temperature,

which initially caused a temporary increase of 5 °C. After heating for 18 hr, the solution was concentrated under reduced pressure. The residue was dissolved in EtOAc (6 L). The organic mixture was washed with a saturated NaCl solution (4 x 2 L), cooled in a MeOH/ice bath (~5 °C) and treated with Et_3N (580 mL, 4.16 mol). After 20 min, the resulting white solid was removed by filteration and washed with EtOAc (1.5 L). The combined EtOAc mixtures were concentrated under reduced pressure until a solid began to precipitate, then the mixture was treated with hexane (4 L). The resultant solid was removed by filtration and air-dried to provide 1-fluoro-4-{[(E)-2-phenylethenyl]sulfonyl}benzene as a white crystalline compound (769 g, 94%): ^{1}H-NMR ($CDCl_3$): δ 6.85 (d, J = 15.1 Hz, 1H); 7.22 (dd, J = 8.7, 8.7 Hz, 2H); 7.44 (m, 5H); 7.69 (d, J = 15.1 Hz, 1H); 7.97 (dd, J = 5.1, 8.7 Hz, 2H); GC-MS (negative ionizaton) *m/z* 262 (M^-). Anal. Calcd for $C_{14}H_{11}FO_2S$: C, 64.11; H, 4.23; F, 7.24; S, 12.22. Found: C, 63.99; H, 4.24; F, 7.43; S, 12.16.

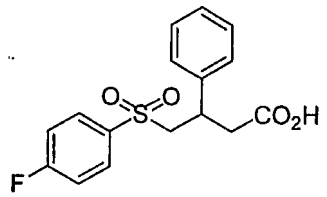
A3a Step 2



A suspension of potassium *tert*-butoxide (420 g, 3.75 mol) in dry dimethylformamide (4300 mL) was treated with dimethyl malonate (445 mL, 3.89 mol) in one portion. An exotherm occurred which raised the internal temperature to 45 °C. The clear yellow solution was stirred at room temperature under argon for 60 minutes, then 1-fluoro-4-{[(E)-2-phenylethenyl]sulfonyl}benzene (892 g, 3.40 mol) was added in one portion. An endotherm occurred which cooled the solution to ~20 °C. The clear yellow solution was stirred at room temperature under argon for 18 hours, at which time TLC analysis (silica gel 60, 25% EtOAc/hexane, UV detection) indicated complete reaction. The contents were poured into a bilayer containing 2 N aqueous HCl (2 L) in a saturated NaCl solution (6 L) and EtOAc (8 L). The organic layer was washed with a saturated NaCl solution (4 x 8 L) and concentrated under reduced pressure to near dryness. The residue crystallized on standing, and was then triturated with hexane (4 mL) and air-dried to afford dimethyl 2-{2-[(4-fluorophenyl)sulfonyl]-1-phenylethyl}malonate (1.31 Kg, 98%) as white crystals: ^{1}H-NMR (DMSO-d_6): δ 3.29 (s, 3H); 3.63 (m, 5H); 3.90 (d, J = 9.7 Hz, 1H); 4.09 (m, 1H); 7.09 (m, 5H); 7.25 (m, 2H); 7.60 (m, 2H). HPLC MS (negative ionization): *m/z* 393 ($(M - 1)^-$).

Anal. Calcd for $C_{19}H_{19}FO_6S$: C, 57.86; H, 4.86; S, 8.13. Found: C, 57.64; H, 4.88; S, 8.11.

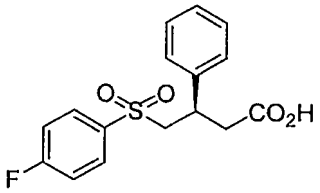
A3a Step 3



A suspension of dimethyl 2-{2-[(4-fluorophenyl)sulfonyl]-1-phenylethyl}malonate (660.0 g, 1.67 moles) in an aqueous 6 N HCl solution (5 L) was heated at the reflux temperature with vigorous stirring for 17 h. The suspension was then slowly cooled to 35 °C with vigorous stirring. The resulting precipitate was removed by filtration, washed with water (4 x 2 L) and dried under reduced pressure (~0.2 torr) at 40 °C to provide 4-[(4-fluorophenyl)sulfonyl]-3-phenylbutanoic acid as a white solid (533 g, 99%): ^{1}H-NMR (DMSO-d_6): δ 2.52 (dd, J = 9.2, 16.2 Hz, 1H); 2.82 (dd, J = 5.6, 16.2 Hz, 1H); 3.43 (m, 1H); 3.74 (dd, J = 5.7, 14.7 Hz, 1H); 3.82 (dd, J = 8.5, 14.7 Hz, 1H); 7.11 (m, 5H); 7.31 (dd, J = 9.1, 9.1 Hz, 2H); 7.72 (dd, J = 5.4, 9.1 Hz, 2H); 12.14 (br s, 1H). HPLC-MS (negative ionization): *m/z* 321 ((M - 1)$^-$). Anal. Calcd for $C_{16}H_{15}FO_4S$: C, 59.62; H, 4.69; F, 5.89; S, 9.95. Found: C, 59.51; H, 4.68; F, 6.02; S, 10.14.

A3b: (3*R*)-4-[(4-Fluorophenyl)sulfonyl]-3-phenylbutanoic acid *via* chiral resolution

A3b Step 1

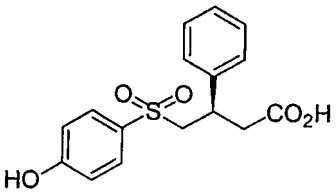


To a solution of 4-[(4-fluorophenyl)sulfonyl]-3-phenylbutanoic acid (145 g, 0.45 mol) in acetonitrile (1.45 L) at room temperature was added (-)-ephedrine (75.0 g, 0.45 mol, 1.0 equiv) in one portion. The solution was then stirred vigorously for 4 h. The resulting thick suspension was filtered, the solids were washed with acetonitrile (2x150 mL) and dried under reduced pressure for 18 hours to give (3*R*)-4-[(4-fluorophenyl)sulfonyl]-3-phenylbutanoic acid ephedrine salt (114 g, 52%, 60% e.e. by chiral HPLC). The ephedrine

salt was recrystallized using acetonitrile (1250 mL) to give (3*R*)-4-[(4-fluorophenyl)sulfonyl]-3-phenylbutanoic acid ephedrine salt (84.6 g, 93.4% e.e.).

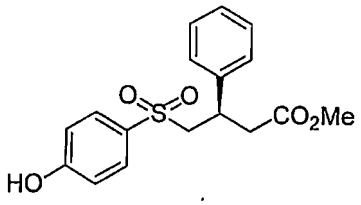
To a vigorously stirred suspension of the ephedrine salt in CH_2Cl_2 (1100 mL) was added a 1N HCl solution (1 L). The resulting mixture was stirred for 15 min and the aqueous layer was extracted with CH_2Cl_2 (500 mL). The combined organic layers were washed with water (2x600 mL) and a saturated NaCl solution (600 mL), dried (Na_2SO_4) and concentrated to a thick slurry (about 150 mL). The white slurry was cooled in a freezer (-14 °C) for 1 h. The solids were collected by filtration, washed with a small amount of cold CH_2Cl_2 and dried under reduced pressure to give (3*R*)-4-[(4-fluorophenyl)sulfonyl]-3-phenylbutanoic acid as a white solid (50.6 g, 99.5% e.e., 34.8% overall yield).

A3b Step 2



A solution of (3*R*)-4-[(4-fluorophenyl)sulfonyl]-3-phenylbutanoic acid (48.1 g, 149 mmol) in a 1N NaOH solution (1 L) was heated at the reflux temperature for 22 h, cooled to 0 °C and acidified to pH 1-2 using conc. HCl. The precipitate was filtered and washed with water. The solid was dissolved in EtOAc (1 L) and the layers were separated. The organic layer was washed with a saturated NaCl solution (300 mL). The combined aqueous layers were back-extracted with EtOAc (500 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give (3*R*)-4-[(4-hydroxyphenyl)sulfonyl]-3-phenylbutanoic acid (43.9 g) as a white solid. The acidic filtrate was extracted with EtOAc (1 L) to give additional product (3.3 g, total 47.2 g, 99%): TLC (0.5% AcOH/2% MeOH/CH_2Cl_2) R_f 0.14; ^{1}H NMR (DMSO-d_6) δ 2.52 (dd, *J*=6.3, 16.1 Hz, 1H), 2.81 (dd, *J*=5.0, 16.0 Hz, 1H), 3.34-3.68 (m, 3H), 6.80-6.85 (m, 2H), 7.08-7.20 (m 5H), 7.50-7.54 (m, 2H), 10.52 (s, 1H), 12.1 (br s, 1H).

A3b Step 3

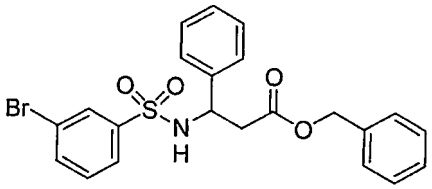


To a 0 °C solution of (3*R*)-4-[(4-hydroxyphenyl)sulfonyl]-3-phenylbutanoic acid (47.2 g, 147 mmol) in MeOH (1 L) was added chlorotrimethylsilane (41 mL, 324 mmol, 2.2 mol). The reaction mixture was allowed to warm to room temperature, stirred for 3 days and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, diluted with hexanes and concentrated under reduced pressure to give methyl (3*R*)-4-[(4-hydroxyphenyl)sulfonyl]-3-phenylbutanoate (48.8 g, 99%) as an off-white solid: TLC (0.5% AcOH/2% MeOH/CH_2Cl_2) R_f 0.51; ^{1}H NMR (DMSO-d_6) δ 2.61 (dd, *J*=9.3, 16.0 Hz, 1H), 2.92 (dd, *J*=5.0, 16.0 Hz, 1H), 3.35-3.71 (m, 6H), 6.81 (d, *J*=8.7 Hz, 2H), 7.09-7.20 (m, 5H), 7.53 (d, *J*=8.7 Hz, 2H), 10.53 (s, 1H).

A4. Synthesis of 3-Arylsulfonylamido-3-arylpropionate Analogues Reaction of 3-Aminopropionate esters:

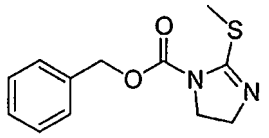
A4a:

A4a Step 1



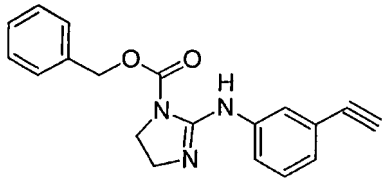
To a solution of benzyl 3-amino-3-phenylpropionate (3.00 g) in dry CH_2Cl_2 (35 mL) at room temperature was added 3-bromobenzenesulfonyl chloride (3.30 g) followed by the dropwise addition of Et_3N (1.80 mL). The homogenous mixture was stirred at room temperature for 72 h, then was concentrated under reduced pressure. The oily residue was dissolved in EtOAc (75 ml) and stirred 20 h at room temperature. The white solids were removed by filtration and the filtrate was concentrated under reduced pressure. The residual material was purified by silica gel chromatography (EtOAc/hexane) to give the desired sulfonamide as an oil, which was crystallized to give a white solid (4.60 g, 83%): mp 79 °C; TLC (20% EtOAc/hexane) R_f = 0.28.

A4a Step 2



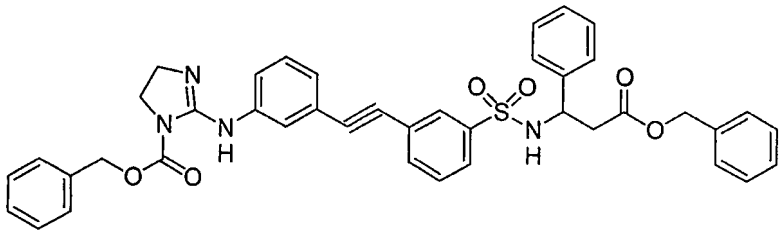
To a solution of 2-methylthio-2-imidazoline hydroiodide (80.8 g) and $NaHCO_3$ (91.8 g) in H_2O (700 mL) at 0 °C was added benzylchloroformate (62.14 g) dropwise over 1h. The resulting mixture was warmed to room temperature and stirred 20 h, then cooled to 10 °C and filtered. The resulting white solid was washed thoroughly with H_20 at 5 °C (4x500 mL) then dried in vacuo under P_2O_5 to a constant weight. The white solid was dissolved in minimal EtOAc at 65 °C (150 mL) and recrystallized at –20 °C to yield 2-thiomethylimidazole as white crystals (45.0 g, 54%): mp 61 °C TLC (50% EtOAc/hexane) R_f 0.20; HPLC ES-MS *m/z* 251 $((M+1)^+)$.

A4a Step 3



A mixture of 3-aminophenylacetylene (94 mg) and the 2-thiomethylimidazole (200 mg) was stirred to homogeneity then heated to a melt under argon at 120 °C for 1 h. TLC indicated the presence of starting materials. More of the 2-thiomethylimidazole (800 mg) was added and the reaction was heated at 120 °C for 16 h. The neat reaction mixture was purified by silica gel chromatography (hexane/EtOAc) to give the desired phenylacetylene as a white solid (134 mg, 52%): TLC (33% EtOAc/hexane) R_f 0.45; HPLC ES-MS *m/z* $((M+1)^+)$.

A4a Step 4

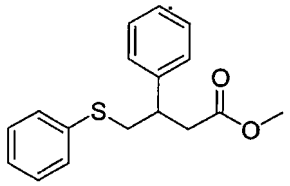


To a solution of the sulfonamide (466 mg) and the phenylacetylene (285 mg) in a mixture of

anh DMF (6 mL) and anh Et_3N (6 mL) was added CuI (43 mg), *trans*-$(Ph_3P)_2PdCl_2$ (157 mg), and Ph_3P (59 mg). The reaction was stirred under argon heating to 80 °C over 0.5 h, then was held at 80 °C for 1h. The reaction was treated with H_2O (200 mL) and extracted with Et_2O (3x300 mL). The ether extracts were washed with a saturated NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/EtOAc) to afford the desired diphenylacetylene (350 mg, 55%): TLC (50% EtOAc/hexane) R_f 0.60; HPLC ES-MS: 713 ($(M+1)^+$).

A5. Synthesis of 3-Arylsulfanylamido-3-arylbutanoate Analogues.

A5a. Methyl 3-Phenyl-4-phenylthiobutanoate



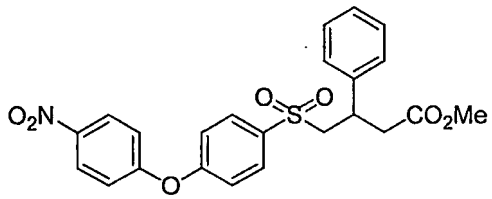
To a –70 °C solution of benzenethiol (6.37 mL, 62.1 mmol) dissolved in Et_2O (40 mL) and THF (20 mL) was added *n*BuLi (2.5M in hexanes, 23.64 mL, 59.1 mmol) over 15 min. The reaction was allowed to warm to room temperature and stirred for 1h. The reaction solution was concentrated and DMF (100 mL) was added followed by the addition of 4-phenyldihydro-2(3H)-furanone. The reaction was heated to 60 °C for 12 h and was cooled to room temperature followed by quenching with 0.1 N HCl. The solution was washed with H_2O (100 mL) and the aqueous phase was back-extracted with EtOAc (100 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated in vacuo and placed on high vacuum to remove traces of DMF. The crude acid was dissolved in MeOH (100 mL) and conc. HCl (2 mL) was added and the reaction was refluxed for 20 h, cooled then concentrated. The crude organic residue was purified by flash silica chromatography (15% EtOAc/hexane) to afford methyl 3-phenyl-4-phenylthiobutanoate as a white powder (11.07 g, 62% over 2 steps): ^1H NMR ($CDCl_3$) δ 7.34-7.17 (m, 10 H), 3.57 (s, 3 H), 3.38-3.35 (m, 1 H), 3.22-3.18 (m, 2 H), 2.98 (dd, J = 16.07, 6.66 Hz, 1 H), 2.68 (dd, J = 15.77, 8.76 Hz, 1 H); TLC (EtOAc/Hex, 3/17) R_f 0.60.

B. General Methods for Synthesis of Phenylamines

B1. General Method for Coupling of Hydroxyphenylsulfones with

Fluoronitrobenzene: Methyl 4-{[4-(4-Nitrophenoxy)phenyl]sulfonyl}-3-phenylbutanoate

B1 Step 1

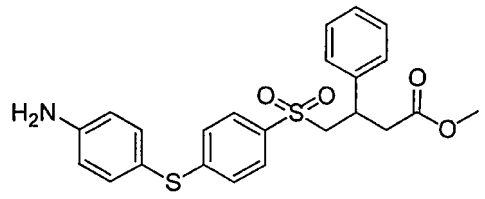


4-Nitrofluorobenzene (4.0 g, 28.2 mmol) and K_2CO_3 (3.90 g, 28.2 mmol) were added to the methyl 4-[(4-hydroxyphenyl)sulfonyl]-3-phenylbutanoate (3.15 g, 9.4 mmol) in DMF (40 mL). The solution was heated to 80 °C for 18 h then cooled to room temperature. The solution was then diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with a saturated NaCl solution then dried over Na_2SO_4. The solution was filtered and concentrated *in vacuo* to give 2.82 g of a yellow oil. The oil was purified by flash chromatography (gradient from 25% EtOAc/75% hexanes to 40% EtOAc/60% hexanes) to give 3.75 g (88%) of the diphenyl ether as a white powder.

B2. General Method for Coupling of an Aminobenzenethiol with a Fluorophenylsulfone

B2a: Methyl 4-({4-[(4-Aminophenyl)thio]phenyl}sulfonyl)-3-phenylbutanoate

B2a Step 1

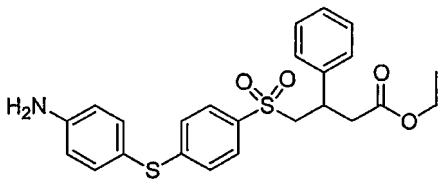


A solution of 4-aminobenzenethiol (0.37 g, 3.0 mmol, 1 equiv) in. DMF (20 mL) was treated with NaH (78 mg, 3.3 mmol, 1.1 equiv), stirred for 40 min, then treated with methyl 4-[(4-fluorophenyl)sulfonyl]-3-phenylbutanoate (1.0 g, 3.0 mmol). The reaction mixture was stirred for 21 h, quenched with H_2O (100 mL) and extracted with EtOAc. The organic layer was washed with a 0.2 N aqueous HCl solution (2 x 100 mL), dried (Na_2SO_4) and

concentrated under reduced pressure. The crude mixture was purified by flash chromatography (100 g SiO_2, gradient from 5% EtOAc/CH_2Cl_2 to 10% EtOAc/CH_2Cl_2) to afford methyl 4-({4-[(4-aminophenyl)thio]phenyl}sulfonyl)-3-phenylbutanoate (1.10 g, 84%) as a white solid: TLC (30% EtOAc/hex) R_f 0.14; ^{1}NMR ($CDCl_3$) δ 2.72 (dd, J_1 = 8.4 Hz, J_2 = 16.2 Hz, 1H), 3.01 (dd, J_1 = 5.5 Hz, J_2 = 16.2 Hz, 1H), 3.39 (dd, J_1 = 6.3 Hz, J_2 = 14.3 Hz, 1H), 3.51-3.57 (m, 4H), 3.67-3.74 (m, 1H), 3.97 (s, 2H), 6.74 (dd, J_1 = 6.6 Hz, J_2 = 1.5Hz, 2H), 7.05 (dd, J_1 = 7.0 Hz, J_2 = 8.4 Hz, 4H), 7.20-7.24 (m, 3H), 7.32 (dd, J_1 = 6.6 Hz, J_2 = 1.5 Hz, 2H), 7.54 (dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 2H) ES-LCMS *m/z* (rel abundance) 442 ($(M+1)^+$).

B2b: Ethyl 4-{[4-(4-aminophenylthio)phenyl]sulfonyl}-3-phenylbutanoate

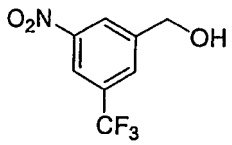
B2b Step 1



To a 0 °C solution of ethyl 4-[(4-bromophenyl)sulfonyl]-3-phenylbutanoate (1.4 g, 3.4 mmol) and 4-aminobenzenethiol (0.43 g, 3.4 mmol, 1 equiv) in anh. DMF (20 mL) was added K_2CO_3 (1.0 g, 7.2 mmol, 2 equiv). The reaction mixture was heated at 80 °C for 17 h, treated with 4- aminobenzenethiol (0.43 g, 3.4 mmol, 1 equiv) and continued heating for 6 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with H_2O (2 x 100 mL). The combined aqueous layers were back-extracted with EtOAc (50 mL). The combined organic layers were washed with a 0.2 N HCl solution (2 x 100 mL), a saturated NaCl solution (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient from 30% to 50% EtOAc/hex) to give ethyl 4-{[4-(4-aminophenylthio)phenyl]sulfonyl}-3-phenylbutanoate (0.80 g, 52%) as a white solid: TLC (40% EtOAc/hex) R_f 0.47; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3H), 2.69 (dd, J = 8.7, 15.7 Hz, 1H), 2.98 (dd, J = 5.8, 15.5 Hz, 1H), 3.39 (dd, J = 6.6, 14.4 Hz, 1H), 3.53 (dd, J = 7.3, 14.4 Hz, 1H), 3.68-3.74 (m, 1H), 3.93-4.05 (m, 4H), 6.72-6.76 (m, 2H), 7.01-7.08 (m, 4H), 7.17-7.27 (m, 3H), 7.30-7.35 (m, 2H), 7.51-7.58 (m, 2H).

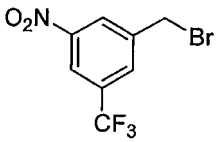
B3 General Method for Coupling of Benzyl Electrophiles with Phenols: Methyl 3-(3,5-Dichlorophenyl)-4-[(4-{[3-nitro-5-(trifluoromethyl)benzyl]oxy}phenyl)sulfonyl]butanoate

B3 Step 1



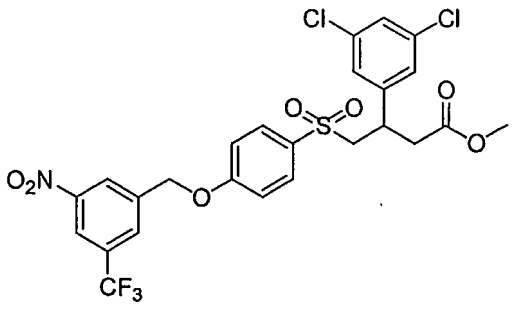
A solution of 3-nitro-5-(trifluoromethyl)benzoic acid (5.81 g, 24.7 mmol) in tetrahydrofuran (70 mL) was slowly treated with borane methyl sulfide complex (29.7 mL, 29.6 mmol), and the mixture was held at the reflux temperature for 6 hours. The mixture was then cooled to room temperature and quenched with methyl alcohol (100 mL). Reaction mixture was concentrated under reduced pressure to afford a yellow oil which was passed through silica gel plug to isolate 5-nitro-3-(trifluoromethyl)phenyl]methan-1ol as pale yellow oil (4.46 g): TLC (40% EtOAc/Hex) R_f 0.51.

B3 Step 2



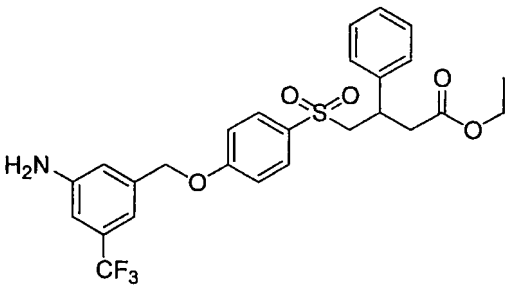
A solution of [5-nitro-3-(trifluoromethyl)phenyl]methanol (4.46 g, 20.16 mmol) in Et_2O (30 mL) was stirred vigorously as it was treated with carbon tetrabromide (7.09 g, 21.37 mmol) followed by slow addition of PPh_3 (5.61g, 21.37 mmol). This mixture was stirred at room temperature overnight. The resulting slurry was filtered and concentrated under reduced pressure to afford an orange oil. The oil was passed through silica gel plug to afford [5-nitro-3-(trifluoromethyl)phenyl]methyl bromide as a pale yellow oil (5.26 g, 92%): TLC (10% EtOAc/hexane) R_f0.80; ^{1}H NMR ($CDCl_3$) δ 8.43-8.45 (d, 2H); 7.95 (s, 1 H); 4.58 (s, 2 H). HPLC ES-MS *m/z* 284 ($(M+1)^+$).

B3 Step 3



A solution of 0.13 g of [5-nitro-3-(trifluoromethyl)phenyl]methyl bromide, phenol (0.17 g, 0.42 mmol) and 0.27 g of $CsCO_3$ (0.84 mmol) in 10 mL of acetone was heated at the reflux tempereature for 1 h. The heat was removed and mixture was partitioned between EtOAc and an aqueous 1 M HCl solution. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography column (50% EtOAc/hexane) to give methyl 3-(3,5-dichlorophenyl)-4-[(4-{[3-nitro-5-(trifluoromethyl)benzyl]oxy}phenyl)sulfonyl]butanoate (0.30 g, 88%).

B3 Step 4

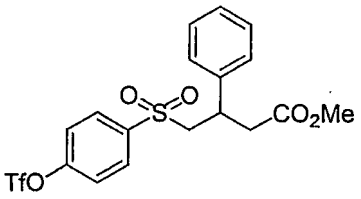


Ethyl 3-(phenyl)-4-[(4-{[3-nitro-5-(trifluoromethyl)benzyl]oxy}phenyl)sulfonyl]butanoate (0.800 g, 1.53 mmol) was dissolved in CH_3CN (7 mL), treated with diphenyl cyanocarbonimidate (0.37 g, 1.53 mmol), and heated at the reflux temperature for 7 days. This mixture was then cooled to room temperature and concentrated under reduced pressure to afford a brown oil. The residue was diluted with CH_2Cl_2 (10 mL). A third of this material was treated with 3-(aminomethyl)pyridine (0.0519 mL, 0.00051 mmol) heated to 60 °C, and stirred overnight. Reaction mixture was cooled to room temperature, and concentrated to an oily residue under reduced pressure. Purification by plug filtration column chromatography (EtOAc) afforded ethyl 3-(phenyl)-4-[(4-{[3-amino-5-(trifluoromethyl)benzyl]-oxy}phenyl)sulfonyl]butanoate (0.226 g, 93%) as a white solid.

B4 General Method for Suzuki Coupling of Organoboronates with Aryl Triflates

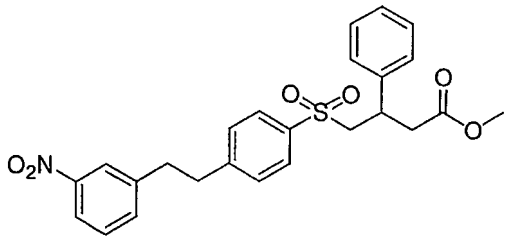
B4a: Methyl 4-({4-[2-(3-Nitrophenyl)ethyl]phenyl}sulfonyl)-3-phenylbutanoate

B4a Step 1



A suspension of methyl 4-[(4-hydroxyphenyl)sulfonyl]-3-phenylbutanoate (521.0 g, 1.56 mol) in dry CH_2Cl_2 (7500 mL) was treated with dry pyridine (165 mL, 161.37 g, 2.04 moles), followed by dropwise addition of trifluoromethanesulfonic anhydride (340 mL, 570 g, 2.02 moles) at 5 °C at a rate that maintained the internal temperature below 15 °C. The reddish-orange solution was stirred at room temperature for 90 minutes, at which time TLC (silica gel 60, 40% EtOAc/hexane, UV detection) analysis suggested complete reaction. The solution was washed with a saturated NaCl solution (4 L), dried (Na_2SO_4) and concentrated to provide methyl 3-phenyl-4-[(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)sulfonyl]butanoate (728 g, 1.56 moles, 100%) as a pale-pink solid. ^{1}H-NMR ($CDCl_3$): 2.72 (dd, J = 7.8, 16.0 Hz, 1H, -$CH_2CO_2CH_3$); 2.89 (dd, J = 6.5, 16.0 Hz, 1H); 3.56 (dd, J = 7.8, 14.4 Hz, 1H); 3.59 (s, 3H); 3.67 (dd, J = 5.9, 14.4 Hz, 1H, -SO_2CH_2-); 3.77 (m, 1H); 7.03 (m, 2H); 7.15 (m, 3H); 7.28, 7.76 (AA'BB' quartet, 4H). Anal. Calcd for $C_{18}H_{17}F_3O_7S_2 \bullet 0.50\ H_2O$: C, 45.47; H, 3.82; F, 11.99; Found: C, 45.44; H, 3.61; F, 11.77.

B4a Step 2



A solution of 9-BBN (0.5 M in THF, 3.44 L) was added to 3-nitrostyrene (256.0 g, 1.72 moles) at -5 °C under argon at a rate that maintained the internal temperature below -2 °C. After final addition, the suspension was allowed to warm to room temperature. A clear

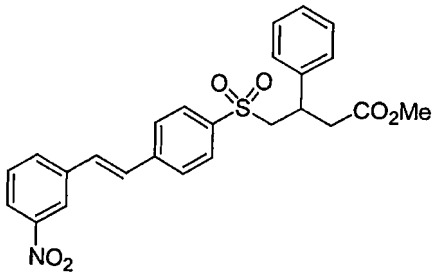
yellow solution was observed after 2 hours. Stirring was continued for 14 hours, at which time, TLC (silica gel 60, 10% EtOAc/hexane, UV detection) suggested complete reaction of the hydroborate and loss of the nitrostyrene. The yellow solution was treated with THF (3.3 L), Et_3N (1.00 L, 726.0 g, 7.17 moles) and methyl 3-phenyl-4-[(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)sulfonyl]butanoate (727 g, 1.56 moles). The resultant solution was degassed with a brisk stream of argon below the medium surface for 20 minutes, prior to addition of the catalyst (40.0 g, 48.98 mmol, ~3 mole%) and degassed water (980 mL). The solution immediately turned reddish-purple, then very dark purple, and an exotherm occurred which increased the internal temperature to 42 °C. The mixture was stirred at room temperature for 60 minutes, at which time TLC (silica gel 60, 40% EtOAc/hexane, UV detection) suggested complete reaction. The dark solution was concentrated and the solids were redissolved in CH_2Cl_2 (6000 mL). The organics were washed with a saturated NaCl solution (2x2 L) and treated with silica gel (3000 g). The silica mix was concentrated, divided into three batches and each batch was placed onto a plug of silica gel (200 g). The product was eluted from each batch (gradient from 20% EtOAc/hexane to 100% EtOAc) to provide a yellow semi-solid. This material was triturated with methanol (4 L) to afford methyl 4-({4-[2-(3-nitrophenyl)ethyl]phenyl}sulfonyl)-3-phenylbutanoate (251 g, 537 mmol) as a yellow solid: ^{1}H-NMR ($CDCl_3$): 2.75 (dd, J = 8.6, 15.9 Hz; 1H); 3.04 (m, 5H); 3.43 (dd, J = 6.1, 14.3 Hz, 1H); 3.57 (m, 4H); 3.72 (m, 1H); 7.09 (dd, J = 2.0, 8.0 Hz, 2H); 7.21 (m, 5H); 7.46 (m, 2H); 7.71 (AA'BB' quartet, J = 8.1 Hz, 2H); 8.08 (m, 2H). Mass spectrum (HPLC/ES) *m/e* 485 ($(M+NH_4)^+$). Anal. Calcd for $C_{25}H_{25}NO_6S$: C, 64.23; H, 5.39; N, 3.00; S, 6.86. Found: C, 64.59; H, 5.29; N, 2.73; S, 6.73.

The filtrate was concentrated to give methyl 4-({4-[2-(3-aminophenyl)ethyl]phenyl}sulfonyl)-3-phenylbutanoate (328 g, 750 mmol) as a dark yellow oil. ^{1}H-NMR (DMSO-d_6): δ 2.65 (dd, J = 9.3, 16.0 Hz, 1H); 2.73 (m, 2H); 2.90 (m, 2H-); 2.94 (dd, J = 5.6, 16.0 Hz, 1H); 3.43 (s, 3H); 3.45 (m, 1H); 3.72 (m, 2H); 6.38 (m, 2H); 6.45 (m, 1H); 6.90 (t, J = 7.8 Hz, 1H); 7.12 (m, 5H); 7.36, 7.61 (AA'BB' quartet, J = 8.7 Hz, 4H). Mass spectrum (HPLC/ES) *m/z* 438 ($(M+1)^+$); 875 ($(2M+1)^+$). The combined materials gave an overall yield for this process of 83%.

B5 General Method for Heck Coupling of Styrenes with Aryl Electrophiles

B5a: Methyl 4-({4-[(*E*)-2-(3-Nitrophenyl)ethenyl]phenyl}sulfonyl)-3-phenylbutanoate

B5a Step 1

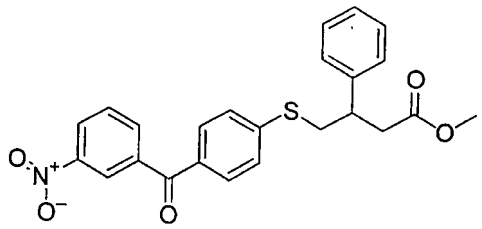


To a solution of methyl 4-[(4-bromophenyl)sulfonyl]-3-phenylbutanoate (5.0 g, 13.0 mmol, 1.0equiv.) in DMF (10ml.) was added a catalytic amount of sodium iodide and the reaction was allowed to stir for 10 min. To this was added 3-nitrostyrene (3.89 g, 26.1 mmol, 2.0 equiv.), palladium acetate (1.0 g, 20 mol%), Et_3N (2.64 g, 26.1 mmol, 2.0 equiv.), and n-Bu_4NCl (1.0 g) and the reaction mixture was heated to 85 ^{0}C overnight. The mixture was cooled to room temperature, diluted with EtOAc, washed with water, dried ($MgSO_4$) and filtered. The organic layer was allowed to evaporate over the 3 days during which crystals formed. The crude product was purified by column chromatography (gradient from 0%-75% EtOAc/ Hex) to yield methyl 4-({4-[(*E*)-2-(3-nitrophenyl)ethenyl]phenyl}sulfonyl)-3-phenylbutanoate (130 mg, 2.2%).

B6. General Method for Friedel-Crafts Acylation Reaction

B6a Methyl 4-([4-(nitrobenzoyl)phenyl]sulfanyl)-3-phenylbutanoate

B6a Step 1



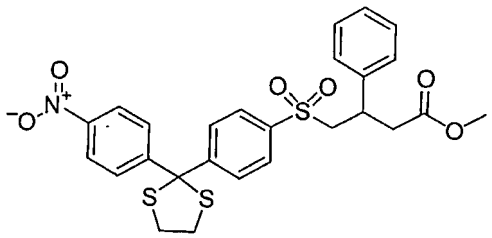
3-Nitrobenzoylchloride (260 mg, 1.40 mmol) was added to a solution of methyl 3-phenyl-4-(phenylsulfanyl)butanoate (400 mg, 1.40 mmol) and 1,2-dichloroethane (35 mL). The

resulting reaction mixture was cooled to 0 °C (ice/H_2O bath) and 1 equivalent of $AlCl_3$ (410 mg, 3.08 mmol) was added. The reaction was allowed to stir for 15 min at this temperature and the cold bath was removed followed by addition of an additional equivalent of $AlCl_3$. The reaction solution turned a dark greenish/yellow and was allowed to stir at room temperature for 18 h, after which time the reaction was treated slowly with H_2O (50 mL). The mixture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (3 x 50 mL), and the combined organic phases were washed with a saturated NaCl solution (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane, 1/4) to afford methyl 4-{4-[(3-nitrophenyl)carbonyl]phenylthio}-3-phenylbutanoate as an oil (320 mg, 53%). TLC (10% MeOH/CH_2Cl_2) *Rf* 0.51; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.17 (m, 13 H), 3.57 (s, 3 H), 3.41-3.33 (m, 1 H), 3.22-3.19 (m, 2 H), 2.99 (dd, J = 15.66, 6.27 Hz, 1 H), 2.68 (dd, J = 15.8, 8.48 Hz, 1 H); HPLC EI-MS *m/z* 436 ($(M+1)^+$).

B7 General Method for the Synthesis of ((Aminophenyl)difluoromethyl)phenylsulfonybutanoates

B7a Methyl 4-({4-[Difluoro(4-nitrophenyl)methyl]phenyl}sulfonyl)-3-phenylbutanoate

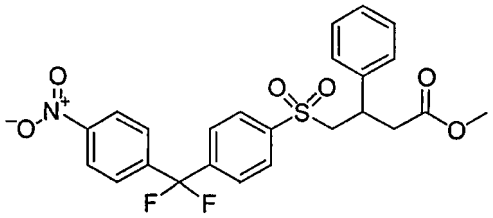
B7a Step 1



Methyl 4-({4-[(4-nitrophenyl)carbonyl]phenyl}sulfonyl)-3-phenylbutanoate (200 mg, 0.656 mmol) was dissolved in CH_2Cl_2 (1 mL) and BF_3·2HOAc (90 μL, 0.656 mmol) was added via syringe. The reaction was allowed to stir for 10 min until all solids had dissolved and then ethanethiol (110 μL, 1.311 mmol) was added slowly via syringe. The reaction was quenched (satd. $NaHCO_3$), extracted with CH_2Cl_2, and the organic phases were combined, dried ($MgSO_4$), filtered, and concentrated to give methyl 4-({4-[2-(4-nitrophenyl)(1,3-dithiolan-2-yl)]phenyl}sulfonyl)-3-phenylbutanoate as a white solid. The resulting crude product was

used without further purification: TLC (10% MeOH/CH_2Cl_2) *Rf* 0.51; ^{1}H NMR ($CDCl_3$) δ 8.54-8.53 (t, 1 H), 8.14-8.10 (m, 1 H), 7.77-7.74 (m, 1 H), 7.66-7.58 (m, 4 H), 7.49-7.44 (t, 1H), 7.20-7.04 (m, 5H), 3.79-3.75 (m, 1H), 3.63-3.44 (m, 4 H), 3.55 (s, 3H), 3.46 (s, 4H), 2.99-2.92 (dd, 1H), 2.76-2.68 (dd, 1H); HPLC EI-MS *m/z* 543 ($(M+1)^+$).

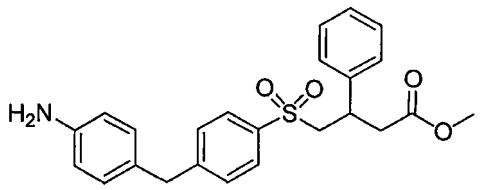
B7a Step 2



A solution of methyl 4-({4-[2-(4-nitrophenyl)(1,3-dithiolan-2-yl)]phenyl}sulfonyl)-3-phenylbutanoate (102 mg, 0.178 mmol) in CH_2Cl_2 (2 mL) was added to a solution of $NO^+BF_4^-$ (46 mg, 0.392 mmol), HF-pyridine (0.4 mL) in CH_2Cl_2 (2 mL) at room temperature. After the addition was complete the reaction was stirred for 1 h at ambient temperature. The reaction mixture was diluted with CH_2Cl_2, passed through a plug column ($Al_2O_3/MgSO_4$, 1/1), and concentrated. The crude organic material was purified by silica gel column chromatography (10% EtOAc/hexane) to afford methyl 4-({4-[difluoro(4-nitrophenyl)methyl]phenyl}sulfonyl)-3-phenylbutanoate (40 mg, 46%). ^{1}H NMR ($CDCl_3$) δ 8.34-8.31 (m, 2 H), 7.79-7.74 (m, 3 H), 7.67-7.62 (m, 1 H), 7.54-7.51 (m, 2 H), 7.12-7.06 (m, 3 H), 7.01-6.98 (m, 2 H, 3.74-3.71 (m, 1H), 3.65-3.46 (m, 5H), 2.94-2.86 (dd, 1H), 2.74-2.66 (dd, 1H); HPLC EI-LRMS *m/z* 490 ($(M+1)^+$).

B8 General Method for the Synthesis of ((Aminophenyl)methyl)phenylsulfonybutanoates

B8a Methyl 4-({4-[(4-Aminophenyl)methyl]phenyl}sulfonyl)-3-phenylbutanoate



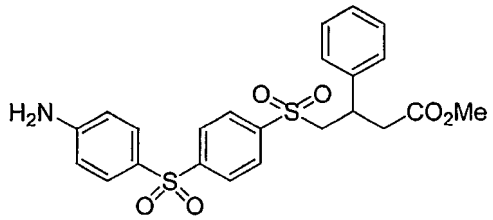
Raney Ni (~1 g) was washed with CH_3OH (4 x 5 ml) until the solution became clear. Methanol (30 mL) was added, followed by methyl 4-({4-[2-(4-nitrophenyl)(1,3-dithiolan-2-

yl)]phenyl}sulfonyl)-3-phenylbutanoate (Procedure B7a, Step 1; 200 mg, 0.369 mmol). The mixture was put under hydrogen atmosphere with stirring for 2 days. The reaction solution was filtered through a pad of Celite and washed with methanol. The solution was concentrated *in vacuo* then purified by silica gel column chromatography (gradient from 25% EtOAc/hexane to 40% EtOAc/hexane) to afford methyl 4-({4-[(4-aminophenyl)methyl]phenyl}sulfonyl)-3-phenylbutanoate (37.4 mg, 23%): TLC (EtOAc) R_f 0.19.

C. General Methods for Interconversion of Phenylamines

C1. General Method for Oxidation of Diphenylsulfides to Diphenylsulfones: Methyl 4-({4-[(4-Aminophenyl)sulfonyl]phenyl}sulfonyl)-3-phenylbutanoate

C1 Step 1

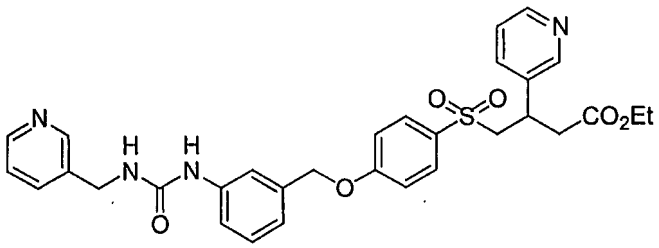


To a solution of methyl 4-({4-[(4-aminophenyl)thio]phenyl}sulfonyl)-3-phenylbutanoate (1.0 g, 2.3 mmol) in $CHCl_3$ (50 mL) was added K_2CO_3 (3.2 g, 23 mmol, 10 equiv) followed by mCPBA (2.0 g, 11.3 mmol, 5 equiv). The resulting mixture was stirred for 4 h and filtered. The filtrate was concentrated and purified by flash chromatography (75 g silica gel, gradient from 10% EtOAc/CH_2Cl_2 to 20% EtOAc/CH_2Cl_2) to afford methyl 4-({4-[(4-aminophenyl)sulfonyl]phenyl}sulfonyl)-3-phenylbutanoate (0.55 g, 51%) as a white solid: TLC (50% EtOAc/hex) R_f 0.38; HPLC ES-MS *m/z* (rel abundance) 474 ($(M+1^+)$).

D. General Methods for Modification of Phenylamines

D1. General Method for Urea Synthesis using Phosgene:

D1a Step 1

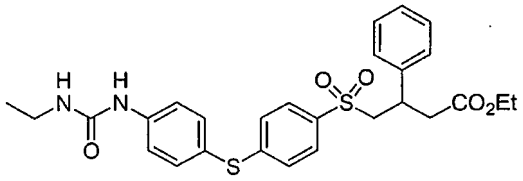


To a solution of ethyl 3-(3-pyridyl)-4-[(4-{[3-aminobenzyl]oxy}phenyl)sulfonyl]butanoate (60 mg, 0.132 mmol), and pyridine (32 uL) inCH_2Cl_2 (3 mL) was added phosgene (20% in toluene, 88 uL) at 0 °C. After stirring at 0 °C for 2 hrs, the mixture was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (3 mL) and 3-(aminomethyl)pyridine (40 uL) was added. The solution was stirred at room temperature overnight. The mixture was purified using column chromatography (MeOH in CH_2Cl_2) to give the desired urea (25 mg, 32%): HPLC ES-MS *m/z* 589 ($(M+1)^+$).

D2. General Method for Urea Synthesis using Isocyanates:

D2a: Ethyl 4-[(4-{4-[(ethylamino)carbonylamino]phenylthio}phenyl)sulfonyl]-3-phenylbutanoate

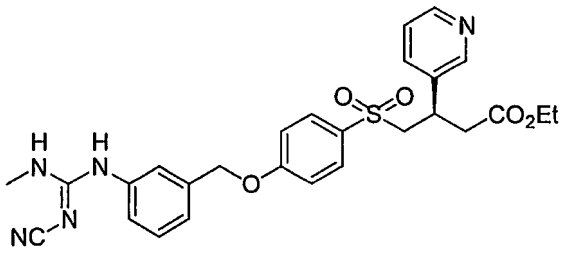
D2a Step 1



A solution of ethyl 4-{[4-(4-aminophenylthio)phenyl]sulfonyl}-3-phenylbutanoate (200 mg, 0.44 mmol) and ethyl isocyanate (72 mg, 1 mmol, 2.3 equiv) in CH_2Cl_2 (5 mL) was stirred at room temperature for 17 h. The reaction mixture was treated with ethyl isocyanate (140 mg, 2 mmol, 4.6 equiv) and heated at 40 °C for 3h. The resulting mixture was treated with ethyl isocyanate (1mL) and stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (40% EtOAc/hex followed by 40% EtOAc/CH_2Cl_2) to yield ethyl 4-[(4-{4-[(ethylamino)carbonylamino]phenylthio}phenyl)sulfonyl]-3-phenylbutanoate (184 mg, 79%) as a white solid: TLC (50% EtOAc/hex) R_f 0.23; ^1H NMR ($CDCl_3$) δ 1.05-1.22 (m, 6H),

2.64 (dd, J = 8.3, 15.7 Hz, 1H), 2.77-2.94 (m, 3H), 3.22 (q, J = 7.1 Hz, 2H), 3.39 (dd, J = 6.6, 14.4 Hz, 1H), 3.50 (dd, J = 7.2, 14.4 Hz, 1H), 3.61-3.68 (m, 1H), 3.96 (q, J = 7.0 Hz, 2H), 6.98-7.02 (m, 4H), 7.10-7.19 (m, 3H), 7.32-7.48 (m, 6H).

D5 General Method for Cyanoguanidine Synthesis: Ethyl 4-({4-[(3-{[(*E*)-(Cyanoimino)(methylamino)methyl]amino}benzyl)oxy]phenyl}sulfonyl)-3-(3-pyridinyl)butanoate



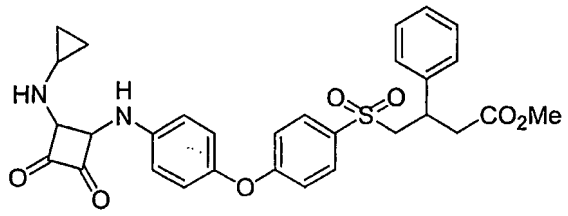
A solution of ethyl 4-({4-[(3-{[(*E*)-methyl]amino}benzyl)oxy]phenyl}sulfonyl)-3-(3-pyridinyl)butanoate (150 mg, 0.33 mmol) and diphenylcyanocarbonimidate (90 mg, 0.38 mmol) in CH_3CN (10 mL) was heated at the reflux temperature for 4 h. The mixture was allowed to cool, and was concentrated under reduced pressure to afford an intermediate: TLC (EtOAc) R_f 0.58. The intermediate was used for next reaction without further purification.

A solution of the crude intermediate (0.165 mmol assumed) and methylamine (2.0 M in THF; 0.2 mL) in THF (3 mL) was heated at 40 °C for 12 hrs. The mixture was then concentrated under reduced pressure, and purified by chromatography (gradient from 50% EtOAc/hexane to 100% EtOAc) to give ethyl 4-({4-[(3-{[(*E*)-(cyanoimino)(methylamino)methyl]amino}benzyl)oxy]phenyl}sulfonyl)-3-(3-pyridinyl)butanoate (69 mg, 0.129 mmol, yield 78%): mp 59-64 °C; TLC (5% MeOH/CH_2Cl_2), R_f 0.20; HPLC ES-MS *m/z* 536 ($(M+1)^+$).

D6 General Method for Squaric Acid Synthesis

D6a: Methyl 4-{[4-(4-{[2-(Cyclopropylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoate

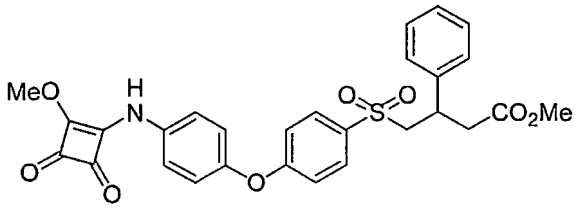
D6a Step 1



3,4-Dimethoxy-3-cyclobutene-1,2-dione (87 mg, 0.58 mmol) was added to a solution of methyl 4-{[4-(4-aminophenoxy)phenyl]sulfonyl}-3-phenylbutanoate (248 mg, 0.58 mmol) in isopropyl alcohol (8 mL). The reaction mixture was heated to 80 °C for 18 h under argon. After cooling, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (60% EtOAc / hex) to give methyl 4-{[4-(4-{[2-(cyclopropylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoate as a yellow foam (150 mg, 48%).

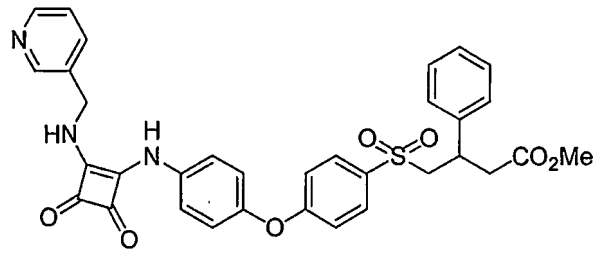
D6b Methyl 4-{[4-(4-{[2-((3-Pyridinylmethylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoate

D6b Step 1



A solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (1.36 g, 9.56 mmol) and methyl 4-{[4-(4-aminophenoxy)phenyl]sulfonyl}-3-phenylbutanoate (3.70 g, 8.69 mmol) in isopropyl alcohol (60 mL) was heated to 80 °C for 18 h under argon. After cooling, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (gradient from 35% EtOAc/hexane to 65% EtOAc/hexane) to give methyl 4-{[4-(4-{[2-((2-pyridinylmethylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoate a yellow-orange solid (3.02 g, 65%).

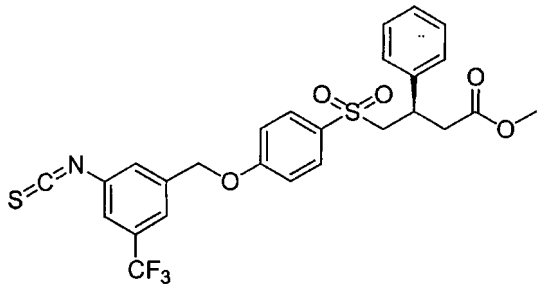
D6b Step 2



A solution of methyl 4-{[4-(4-{[2-((2-pyridinylmethylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoate (3.0 g, 5.6 mmol) and 3-aminomethylpyridine (1.14 ml, 11 mmol) in THF (60 mL) was heated at the reflux temperature under argon. After ~5 min at the reflux temperature, a white precipitate formed. After 18 h, the mixture was cooled to room temperature, concentrated under reduced pressure and the residue was purified by flash chromatography (gradient from1% $MeOH/CH_2Cl_2$ to 5% $MeOH/CH_2Cl_2$) to give methyl 4-{[4-(4-{[2-((3-pyridinylmethylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoate as a yellow solid (2.77 g, 81%).

D7 General Method for the Synthesis of 4,5-Dihydro-1H-imidazol-2-ylamines: Methyl 4-[(4-{[3-(4,5-Dihydro-1H-imidazol-2-ylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)sulfonyl]-3-phenylbutanoate

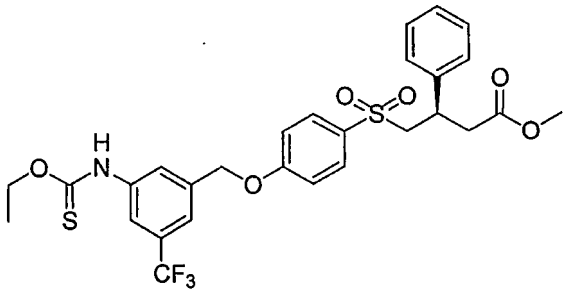
D7 Step 1



Methyl 3-(3,5-dichlorophenyl)-4-[(4-{[3-amino-5-(trifluoromethyl)benzyl]oxy}phenyl)sulfonyl]butanoate (2.5g, 4.93mmol) was dissolved in CH_2Cl_2 (25 mL) and treated with thiophosgene (413 uL, 5.42mmol). The reaction mixture was stirred at room temperature for 2h and then concentrated under reduced pressure. The residue was diluted with EtOAc and passed through silica gel plug to afford methyl (3R)-4-[(4-{[3-isothiocyanato-5-(trifluoromethyl)phenyl]methoxy}phenyl)sulfonyl]-3-

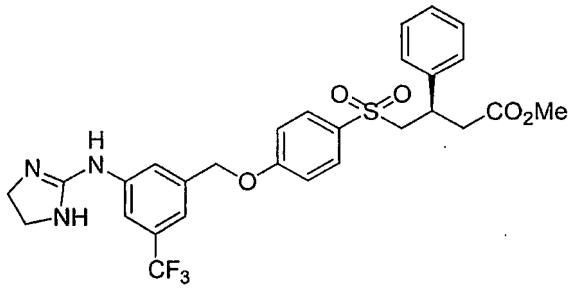
phenylbutanoate.

D7 Step 2



Methyl (3R)-4-[(4-{[3-isothiocyanato-5-(trifluoromethyl)phenyl]methoxy}phenyl)sulfonyl]-3-phenylbutanoate was dissolved in abs. EtOH (30 mL), and allowed to stir at 50 °C for 18 h. Reaction was cooled to room temperature and concentrated under erduced pressure to afford an orange oil. The residue was purified using a silica gel plug (40% EtOAc/ hexanes) to afford methyl (3R)-4-{[4-({3-[(ethoxythioxomethyl)amino]-5-(trifluoromethyl)phenyl}-methoxy)phenyl]sulfonyl}-3-phenylbutanoate as a pale beige solid (1.68 g).

D7 Step 3



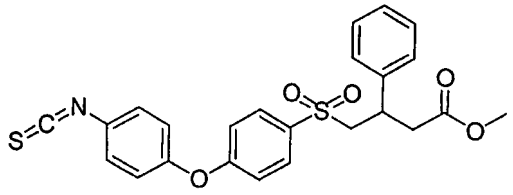
Methyl (3R)-4-{[4-({3-[(ethoxythioxomethyl)amino]-5-(trifluoromethyl)phenyl}methoxy)-phenyl]sulfonyl}-3-phenylbutanoate (1.68 g, 2.82mmol) was diluted with toluene (5 mL) and treated with ethylenediamine (0.186 g, 3.1 mmol). The resulting mixture was heated at 100 °C for 18 h. Reaction was allowed to cool to room temperature, diluted with EtOAc followed by a small amount of MeOH to clear up the turbid reaction mixture. The resulting solution was concentrated to light yellow solids under reduced pressure, redissolved in EtOAc, adsorbed onto silica gel and purified by filtration through a plug of silica gel (gradient from 3% Et_3N/EtOAc to 10% MeOH/3% Et_3N EtOAc) to afford methyl 4-[(4-{[3-(4,5-dihydro-1H-imidazol-2-ylamino)-5-(trifluoromethyl)benzyl]oxy}phenyl)sulfonyl]-3-

phenylbutanoate as a pale beige solid (0.76 g).

D8 General Method for the Synthesis of 2-Thiazolylamines

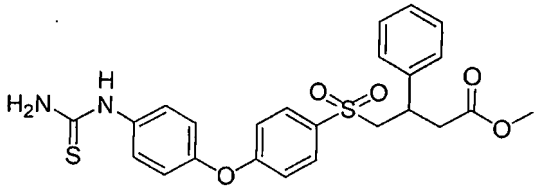
D8a. Methyl 4-({4-[4-(5,6-Dihydro-4H-cyclopenta[d][1,3]thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)-3-phenylbutanoate

D8a Step 1



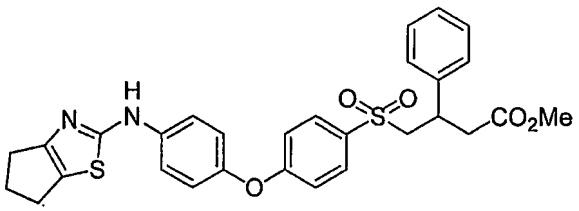
To a solution of methyl 4-{[4-(4-aminophenoxy)phenyl]sulfonyl}-3-phenylbutanoate (3.20 g, 7.52 mmol) in anh. CH_2Cl_2 (70 mL), was added thiophosgene (0.75 mL, 9.8 mmol) under argon. The reaction mixture was stirred 18 h at room temperature, then heated at the reflux temperature for 2 h. Concentration under reduced pressure after cooling to room temperature gave a brown oil. The residue was purified by flash chromatography (10% EtOAc/hexanes) to give methyl 4-{[4-(4-isothiocyanatophenoxy)phenyl]sulfonyl}-3-phenylbutanoate (3.38 g 96%) as a white solid.

D8a Step 2



To a solution of methyl 4-{[4-(4-isothiocyanatophenoxy)phenyl]sulfonyl}-3-phenylbutanoate (3.38 g, 7.2 mmol) in CH_2Cl_2 (70 mL) was added NH_3 (2 M in MeOH, 7.2 mL, 14.5 mmol) under argon. The reaction mixture was stirred overnight at room temperature. Concentration under reduced pressure gave methyl 4-[(4-{4-[(aminothioxomethyl)amino]phenoxy}-phenyl)sulfonyl]-3-phenylbutanoate as a white solid (3.51 g, 100%).

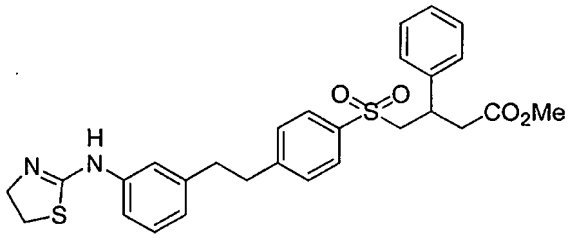
D8a Step 3



To a suspension of methyl 4-[(4-{4-[(aminothioxomethyl)amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoate (2.26 g, 4.66 mmol) in anh benzene (60 mL), was added 2-chlorocyclopentanone (1.50 g, 12.6 mmol). The reaction mixture was heated in the presence of a Dean-Stark trap at the reflux temperature for 6 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc / 80% hexanes) to give methyl 4-({4-[4-(5,6-dihydro-4H-cyclopenta[d][1,3]thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)-3-phenylbutanoate as a foam-like solid (1.72 g, 68%).

D8b: Methyl 4-[(4-{2-[3-(4,5-Dihydro-1,3-thiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoate

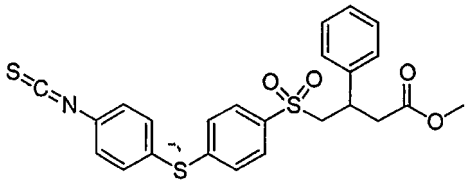
D8b Step 1



A mixture of methyl 4-[(4-{2-[3-aminophenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoate (0.250 g, 0.57 mmol), toluene (3 mL), and thiazoline (0.015 g, 0.114 mmol) were heated at the reflux temperature for 72 h and then concentrated to an oil under reduced pressure. The crude mixture was purified by silica gel chromatography (10% MeOH/$CHCl_3$) to afford methyl 4-[(4-{2-[3-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoate (0.047 g).

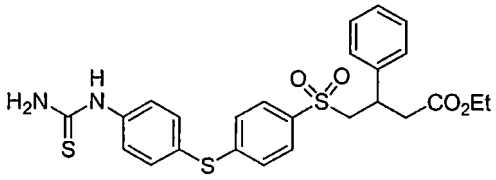
D8c: Ethyl 3-phenyl-4-({4-[4-(1,3-thiazol-2-ylamino)phenylthio]phenyl}sulfonyl)-butanoate

D8c Step 1



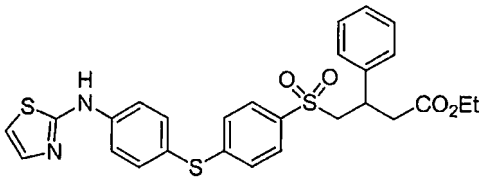
A solution of ethyl 4-{[4-(4-aminophenylthio)phenyl]sulfonyl}-3-phenylbutanoate (102 mg, 0.22 mmol) and thiophosgene (27 mg, 0.23 mmol, 1.05 equiv) in anh. toluene (10 mL) was heated at 80 °C for 2 days. The resulting mixture was allowed to cool to room temperature and concentrated under reduced pressure to give ethyl 4-{[4-(4-isothiocyanatophenylthio)phenyl]sulfonyl}-3-phenylbutanoate as a white solid: TLC (20% EtOAc/hexanes) R_f 0.33.

D8c Step 2



To a solution of crude ethyl 4-{[4-(4-isothiocyanatophenylthio)phenyl]sulfonyl}-3-phenylbutanoate (0.22 mmol) in CH_2Cl_2 (5 mL) was added a 2M solution of NH_3 in EtOH (5 mL, 10 mmol). The reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure to give ethyl 4-[(4-{4-[(aminothioxomethyl)amino]phenylthio}phenyl)sulfonyl]-3-phenylbutanoate: TLC (50% EtOAc/hexanes) R_f 0.35.

D8c Step 3

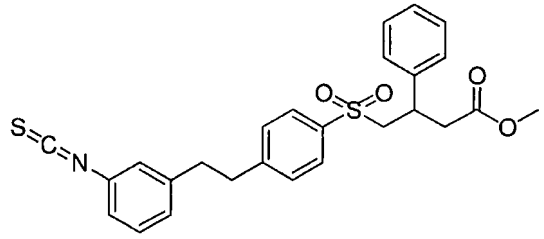


A mixture of crude ethyl 4-[(4-{4-[(aminothioxomethyl)amino]phenylthio}phenyl)sulfonyl]-3-phenylbutanoate (0.22 mmol) and chloroacetaldehyde (50% in water; 1 mL) in benzene (10 mL) was heated in a Dean-Stark apparatus for 4 h. The resulting mixture was purified by flash chromatography (30% EtOAc/hex) to give ethyl 3-phenyl-4-({4-[4-(1,3-thiazol-2-ylamino)phenylthio]phenyl}sulfonyl)butanoate (98 mg, 83% for 3 steps) as an off-white solid: TLC (50% EtOAc/hexanes) R_f 0.19; ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J = 7.2 Hz, 3H), 2.61 (dd, J = 9.0, 15.9 Hz, 1H), 2.89 (dd, J = 5.5, 15.5 Hz, 1H), 3.34 (dd, J = 6.5, 14.3 Hz, 1H), 3.44-3.68 (m, 2H), 3.89-3.98 (m, 2H), 6.67 (d, J = 3.4 Hz, 1H), 6.97-7.03 (m, 4H), 7.09-7.16 (m, 3H), 7.28 (d, J = 3.5 Hz, 1H), 7.38-7.50 (m, 7H).

D9 General Method for the Synthesis of 2-Thiazinylamines

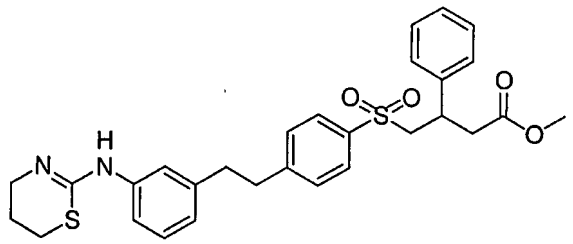
D9a. Methyl 3-Phenyl-4-[(4-{2-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoate

D9a Step 1



To a solution of methyl 4-[(4-{2-[3-aminophenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoate (0.59 g, 1.35 mmol) in CH_2Cl_2 (10 mL) was added thiophosgene (0.17 g; 1.48 mmol) at room temperature. The reaction stirred overnight and was concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford methyl 4-({4-[2-(3-isothiocyanatophenyl)ethyl]phenyl}sulfonyl)-3-phenylbutanoate (0.43 g).

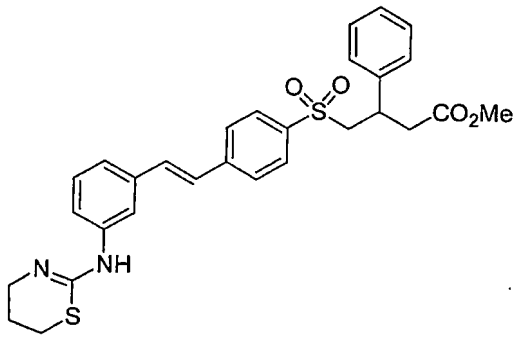
D9a Step 2



Methyl 4-({4-[2-(3-isothiocyanatophenyl)ethyl]phenyl}sulfonyl)-3-phenylbutanoate (0.250 g; 0.521 mmol) was treated with 1-chloropropylamine HCl salt (0.102 g, 0.784 mmol) and Et_3N (0.105 g, 1.04 mmol). The crude product was purified by silica gel chromatography to afford methyl 3-phenyl-4-[(4-{2-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoate (0.185 g).

D9b: Methyl 4-[(4-{2-[3-(5,6-Dihydro-4H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoate

D9b Step 1

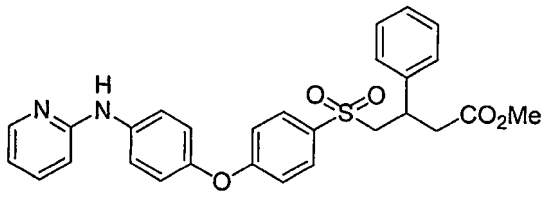


To a mixture of methyl 3-phenyl-4-[(4-{(E)2-[3-(1,3-thiazolin-2-ylamino)phenyl]-ethyl}phenyl)sulfonyl]-butanoate (0.04 g, 0.084 mmol) and chloropropylamine hydrochloride (0.016 g, 0.126 mmol, 1.5 equiv.) in CH_2Cl_2 (5 mL) was added Et_3N (.024 mL, .167 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The crude residue gave methyl 4-[(4-{2-[3-(5,6-dihydro-4H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoate (0.020 g, 44% yield).

D10 General Method for the Synthesis of 2-Pyridinylylamines

D10a. Methyl 3-Phenyl-4-({4-[4-(2-pyridinylamino)phenoxy]phenyl}sulfonyl)butanoate:

D10a Step 1

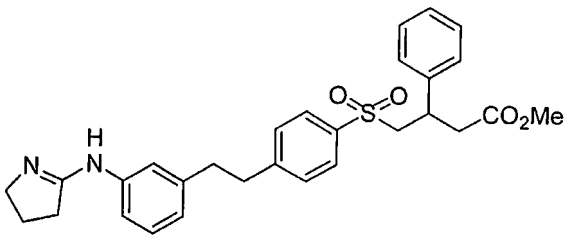


Methyl 3-phenyl-4-({4-[4-aminophenoxy]phenyl}sulfonyl)butanoate (150 mg, 0.35 mmol) and 2-chloropyridine (0.3 mL, 3.1 mmol) were suspended in DMF (2 mL) and heated at the reflux temperature for 18 h. The resulting mixture was concentrated under reduced pressure and the residue purified by flash column chromatography (40% EtOAc/60% hexanes) to give methyl 3-phenyl-4-({4-[4-(2-pyridinylamino)phenoxy]phenyl}sulfonyl)butanoate as a white foam (48 mg, 27%).

D11 General Method for the Synthesis of 3,4-Dihydro-2H-pyrrol-5-ylamines

D11a. Methyl 4-[(4-{2-[3-(3,4-Dihydro-2H-pyrrol-5-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoate:

D11a Step 1

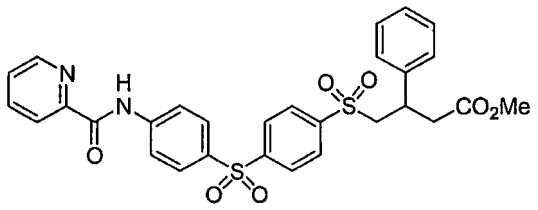


To a solution of methyl 4-[(4-{2-[3-aminophenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoate (0.50, 01.14 mmol) in isopropyl alcohol (5 mL) at 80 °C was added Et_3N (0.16 g, 1.60 mmol) and the electrophile (0.36 g, 1.48 mmol). The reaction mixture was stirred for 72 h at 65 °C and was concentrated under reduced pressure. The residue was purified by column chromatography to afford methyl 4-[(4-{2-[3-(3,4-dihydro-2H-pyrrol-5-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoate (0.050 g).

D12 General Methods for Synthesis Amides from Phenyl Amines

D12a:

D12a Step 1



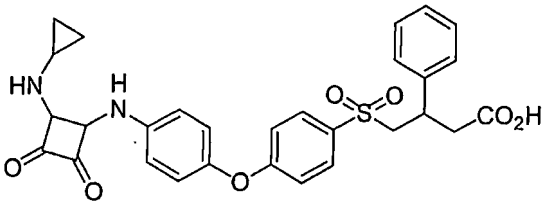
To a solution of picolinic acid (39 mg, 0.32 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL) was added a 2M solution of oxalyl chloride in CH_2Cl_2 (0.2 mL, 0.4 mmol, 2 equiv). The resulting deep red solution was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and treated with a solution of methyl 4-({4-[(4-aminophenyl)sulfonyl]phenyl}sulfonyl)-3-phenylbutanoate (100 mg, 0.21 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature for 3 days. TLC indicated partial reaction. To a solution of picolinic acid (39 mg, 0.32 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL) was added a 2M solution of oxalyl chloride in CH_2Cl_2 (0.2 mL, 0.4 mmol, 2 equiv). The resulting deep red solution was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and added to the reaction mixture, which was then stirred for 4 h. The resulting mixture was diluted with EtOAc (100 mL), washed with a saturated $NaHCO_3$ solution (100 mL), a saturated NaCl solution, dried (Na_2SO_4) and concentrated under reduced pressure to give the desired picolinamide (130 mg, 100%) as a beige solid: TLC (50% EtOAc/hex) R_f 0.27; ^1H NMR ($CDCl_3$) δ 2.56 (dd, J = 7.5, 16.1 Hz, 1H), 2.73 (dd, J = 6.5, 15.6 Hz, 1H), 3.46-3.64 (m, 6H), 3.73 (s, 1H), 6.85 (s, 5H), 7.44-7.48 (m, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.77-7.95 (m, 6H), 8.16 (d, J = 7.5 Hz, 1H), 8.54 (d, J = 4.4 Hz, 1H).

E. General Method for Hydrolysis of Esters to Carboxylic Acids

E1. General Method for KOH Saponification of Esters

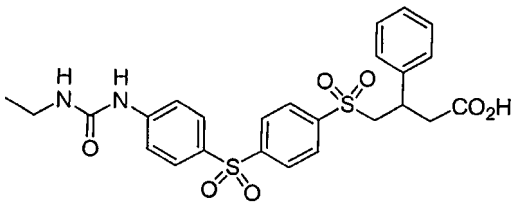
E1a. 4-{[4-(4-{[2-(Cyclopropylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic Acid

E1a Step 1



To a solution of methyl 4-{[4-(4-{[2-(cyclopropylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoate (45 mg, 0.08 mmol) in MeOH (4.5 mL) and water (1.5 mL) was added KOH (300 mg, 5.3 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure and the aqueous solution was neutralized to pH = 6.0 with 1N HCl. The solution was extracted with CH_2Cl_2 and the combined organic layers were washed with a saturated NaCl solution then dried (Na_2SO_4) and concentrated under reduced pressure to give 4-{[4-(4-{[2-(cyclopropylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid as a colorless solid (32 mg, 73%).

E1b: 4-{[4-({4-[(Ethylamino)carbonylamino]phenyl}sulfonyl)phenyl]sulfonyl}-3-phenylbutanoic acid

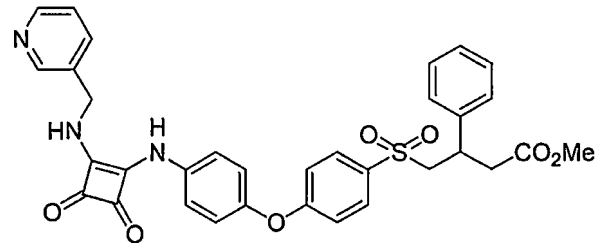


To a solution of ethyl 4-{[4-({4-[(ethylamino)carbonylamino]phenyl}sulfonyl)-phenyl]sulfonyl}-3-phenylbutanoate (142 mg, 0.25 mmol) in MeOH (2 mL) was added a 0.33 M KOH solution (10% H_2O/90% MeOH, 1 mL, 0.33 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature for 2 days, treated with a 1 N HCl solution (1 mL) and concentrated under reduced pressure. The residue was diluted with EtOAc (50 mL), washed with H_2O (25 mL) and a saturated NaCl solution (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give 4-{[4-({4-[(ethylamino)carbonylamino]phenyl}sulfonyl)phenyl]sulfonyl}-3-phenylbutanoic acid (113 mg, 85%) as a white solid: mp 168 °C, dec; TLC (1% AcOH/EtOAc) R_f 0.54; ^{1}H NMR (DMSO-d_6) δ 1.01 (t, J = 7.2 Hz, 3H), 2.40 (dd, J = 8.9, 16.0 Hz, 1H), 2.72 (dd, J = 5.8, 16.1

Hz, 1H), 3.03-3.12 (m, 1H), 3.30-3.44 (m, 2H), 3.74 (dd, J = 4.5, 14.4 Hz, 1H), 3.97 (dd, J = 9.8, 15.1 Hz, 1H), 6.31 (t, J = 5.4 Hz, 1H), 6.72-6.77 (m, 3H), 6.92-6.95 (m, 2H), 7.63-7.67 (m, 4H), 7.79-7.85 (m, 4H), 9.07 (s, 1H), 12.16 (br s, 1H).

E1c: 4-{[4-(4-{[2-((3-pyridinylmethylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanic acid

E1c Step 1

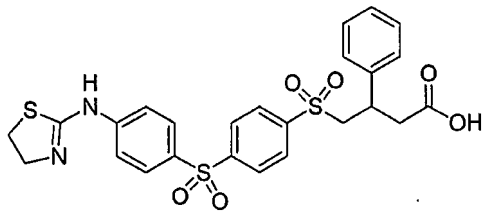


A solution of the compound from Step B (2.50 g, 4.1 mmol) and KOH (245 mg, 6.14 mmol) in MeOH (30 mL) and water (1.5 mL) was stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure and the aqueous solution was brought to pH 2-3 with conc. HCl. The mixture was then further concentrated under reduced pressure and the residue placed under high vacuum. The solid was dissolved into DMF and filtered. The resulting solution was concentrated under reduced pressure and the residue triturated in EtOAc. The suspension was filtered, giving 900 mg of solid. Upon sitting, another 984 mg of solid precipitated from the filtrate and was also collected. The solids were combined, washed with EtOAc, and dried under vacuum to give 4-{[4-(4-{[2-((3-pyridinylmethylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid HCl salt (1.84 g, 72%) as a yellow solid.

E2. General Method for Palladium-Mediated Hydrolysis of Allyl Esters

E2a.

E2a Step 1

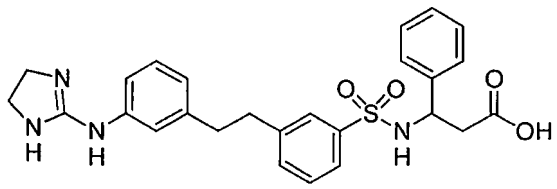


To a 0 °C solution of allyl 4-{[4-({4-[4,5-Dihydro-1,3-thiazol-2-ylamino amino]phenyl}sulfonyl)phenyl]sulfonyl}-3-phenylbutanoate (0.1 g, 0.17 mmol) in CH_3CN (10 mL) was added Pd $(Ph_3P)_4$ (0.05 g, 0.04 mmol, 0.25 equiv), followed by Ph_3P (0.02 g, 0.08 mmol, 0.5 equiv) and pyrrolidine (0.01 g, 0.17 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 2 h, then concentrated under reduced pressure. The residue was purified by HPLC (CH_3CN/H_2O) to give 3-phenyl-4-[(4-{[4-(1,3-thiazolin-2-ylamino)phenyl]sulfonyl}phenyl)sulfonyl]butanoic acid (10 mg, 7%): TLC (0.05% ACOH/ 95.5% ETOAC) RF 0.19; HPLC ES-MS *m/z* 545 $((M+1)^+$, 100%).

E3. General Method for Hydrogenation of Benzyl Esters

E3a. 3-{[(3-{2-[3-(2-Imidazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]amino}-3-phenylpropanoic Acid

E3a Step 1



To a solution of the benzyl ester described in Section A4a Step 4 (300 mg) in MeOH (50 ml) under argon was added 10% Pd/C (600 mg) and the mixture was hydrogenated at 1 atm at room temperature for 6 h. The reaction was filtered through a pad of Celite washing well with MeOH. The MeOH mixture was concentrated under reduced pressure to give crude product (110 mg). The Celite/Pd/C was stirred in 4:4:1 CH3CN/MeOH/H2O (500 ml) for 16 h. This was again filtered through a pad of Celite washing well with MeOH. The MeOH mixture was concentrated under reduced pressure to yield more crude product (50 mg). The combined crude oils were purified by silica gel chromatography (CH_3CN/H_2O). 3 3-{[(3-{2-

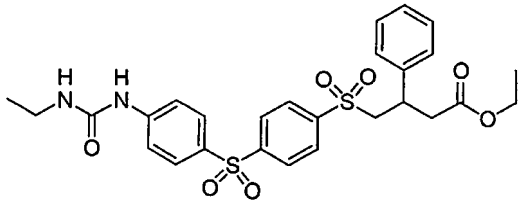
[3-(2-Imidazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]amino}-3-phenylpropanoic acid was obtained as a white powder (62 mg, 30%): TLC 20% H_2O/CH_3CN R_f 0.55; HPLC ES-MS *m/z* ($(M+1)^+$).

F Modification of Final Esters and Acids

F1. General Method for Oxidation of Diphenyl Sulfides

F1a: Ethyl 4-{[4-({4-[(ethylamino)carbonylamino]phenyl}sulfonyl)phenyl]sulfonyl}-3-phenylbutanoate

F1a Step 1



A mixture of ethyl 4-[(4-{4-[(ethylamino)carbonylamino]phenylthio}phenyl)sulfonyl]-3-phenylbutanoate (164 mg, 0.31 mmol) and mCPBA (187 mg, 1.1 mmol, 3.5 equiv) in $CHCl_3$ (5 mL) was stirred at room temperature for 17 h. The resulting mixture was treated with Na_2SO_3 (100 mg, 0.79 mmol, 2.5 equiv) and filtered through a pad of basic alumina (10% MeOH/EtOAc). The filtrate was concentrated under reduced pressure and purified by flash chromatography (70% EtOAc/hex) to give ethyl 4-{[4-({4-[(ethylamino)carbonylamino]-phenyl}sulfonyl)phenyl]sulfonyl}-3-phenylbutanoate (136 mg, 78%) as a white solid: TLC (50% EtOAc/hex) R_f 0.25; HPLC ES-MS m/z 559 (MH^+, 100%); ^1H NMR ($CDCl_3$) δ 1.05-1.14 (m, 6H), 2.65 (dd, J = 7.4, 16.0 Hz, 1H), 2.82 (dd, J = 6.8, 16.1 Hz, 1H), 3.17-3.26 (m, 2H), 3.57-3.76 (m, 3H), 4.01 (q, J = 6.7 Hz, 2H), 5.50 (t, J = 5.5 Hz, 1H), 6.96 (s, 5H), 7.47-7.85 (m, 8H).

F2. General Method for Chiral HPLC Resolution Resolution of Esters and Acids

F2a: 3*R*)-3-Phenyl-4-[(4-{2-[3-(1,3-thiazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic Acid and (3*S*)-3-Phenyl-4-[(4-{2-[3-(1,3-thiazolin-2-ylamino)phenyl]ethyl}-phenyl)sulfonyl]butanoic Acid

F2a Step 1

Racemic 3-phenyl-4-[(4-{2-[3-(1,3-thiazolin-2-ylamino)-phenyl]ethyl}phenyl)sulfonyl]-butanoic acid was separated on Chiralpak AD column (flow rate 24 mL/min, Eluent A: hexane, 0.1% Et_3N, Eluent B: 1:1 MeOH:EtOH, 0.1% Et_3N; Isocratic 75:25 Eluent A: Eluent B for 30 min) to give (3*R*)-3-phenyl-4-[(4-{2-[3-(1,3-thiazolin-2-ylamino)phenyl]ethyl}-phenyl)sulfonyl]butanoic acid ((*R*)-1): Retention Time 7.26 min, followed by (3*S*)-3-phenyl-4-[(4-{2-[3-(1,3-thiazolin-2-ylamino)phenyl]ethyl}-phenyl)sulfonyl]butanoic acid ((*S*)-1): Retention Time 9.86 min.

The compounds of the invention, which include those compounds described by Tables 1 - 8 below, may be prepared by using the above described procedures or known chemical reactions and procedures which are within the purview of one of ordinary skill in the art.

Table 1 (Examples 1- 61) depicts the described compounds wherein L is either CH_2NH or CH_2O and D is CH_2.

Table 2 (Examples 62 and 63) depicts the described compounds wherein L is OCH_2 and D is CH_2.

Table 3 (Examples 64 - 161) depicts the described compounds wherein L is CH_2CH_2, -C=C- or -C≡C- and D is CH_2.

Table 4 (Examples 162 - 174) depicts the described compounds wherein L is C(=O) or C(=N-OCH_3) and D is CH_2.

Table 5 (Examples 175 - 185) depicts the described compounds wherein L is CH_2, CF_2, or CH(OH) and D is CH_2.

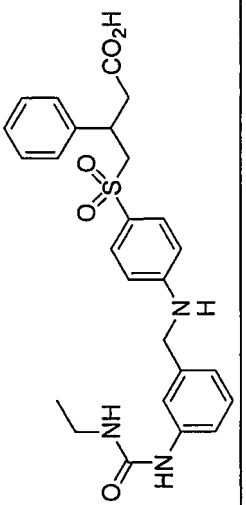
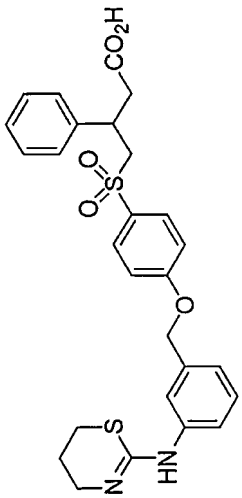
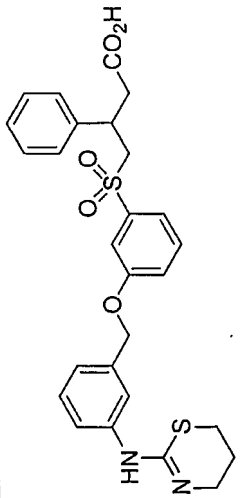
Table 6 (Examples 186 - 275) depicts the described compounds wherein L is O and D is CH_2.

Table 7 (Examples 276 - 290) depicts the described compounds wherein L is S or $S(=O)_2$, and D is CH_2.

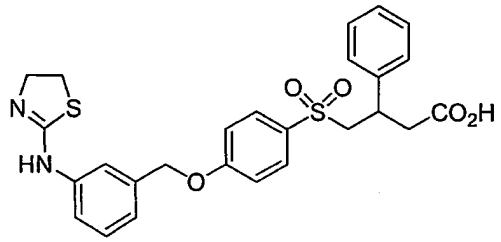
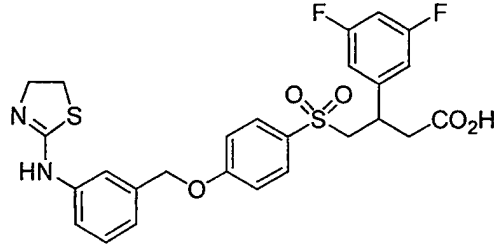
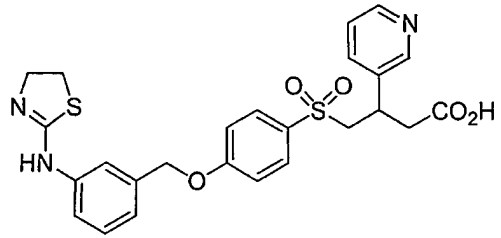
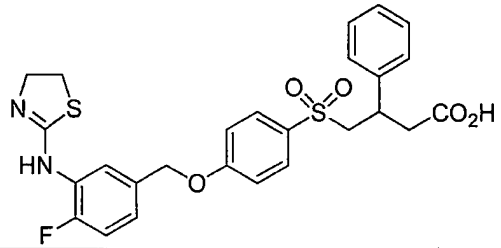
Table 8 (Examples 291 - 305) depicts the described compounds wherein L is CH_2CH_2 and D is NH.

Table 9 lists the IUPAC names of the compounds exemplified in Tables 1-8 as determined using Nomenclator® version 3.01 (ChemInnovation Software, Inc.).

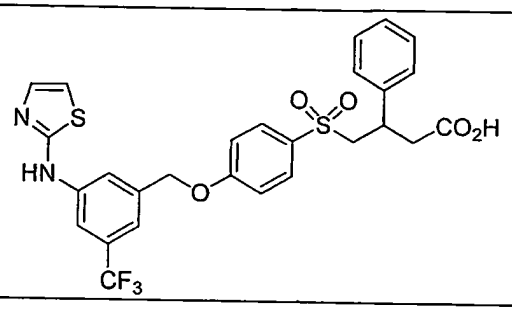
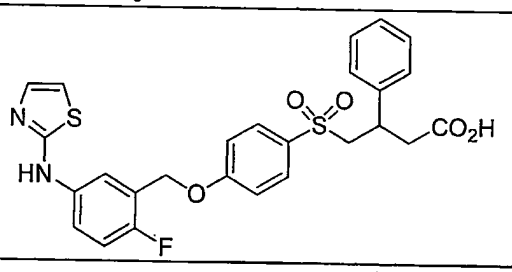
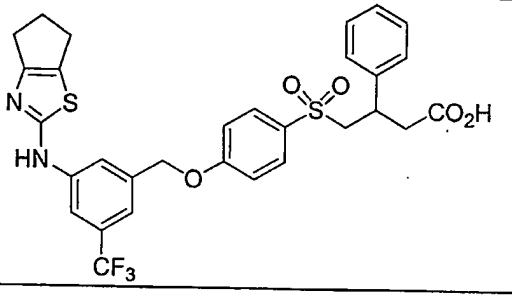
Table 1.

Ex. #	Butyric Acid	mp (°C)	TLC R_f	Solvent System	Mass Spec.	$\alpha v\beta_3$ IC_{50}	$\alpha v\beta_5$ IC_{50}
1			0.53	30% MeOH / 70% EtOAc		b	
2			0.60	20% MeOH / 80% $CHCl_3$		a	
3			0.53	10% MeOH / 90% CH_2Cl_2		a	

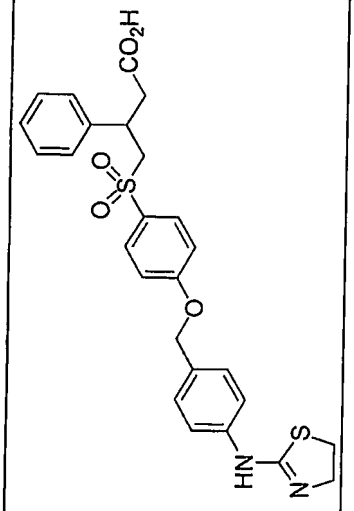
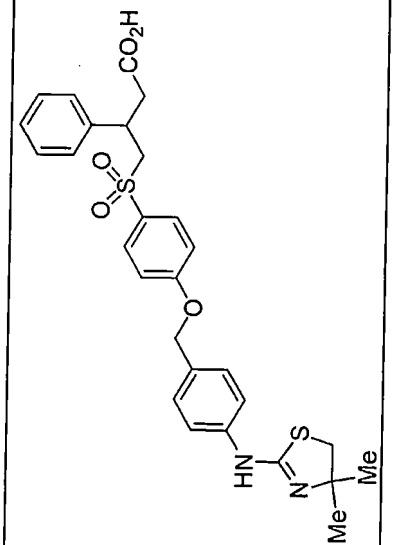
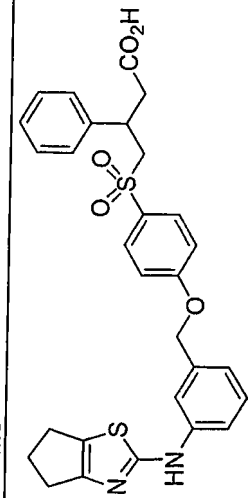
4			0.45	10% MeOH / 90% CH_2Cl_2		a
5			0.45	15% MeOH / 85% CH_2Cl_2		a
6		150-160	0.45	5% MeOH / 95% CH_2Cl_2	579 (M+H)+ [HPLC ES-MS]	a

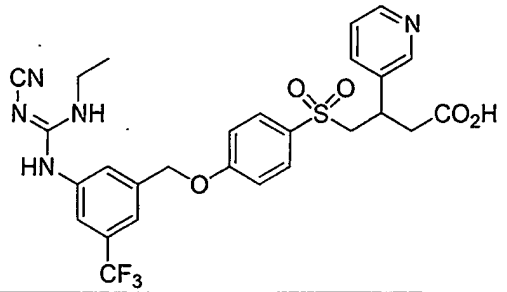
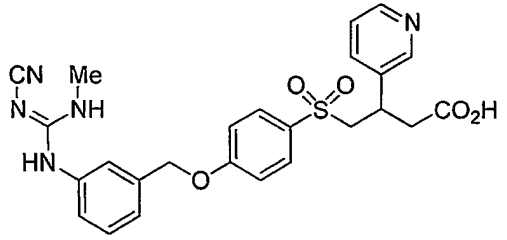
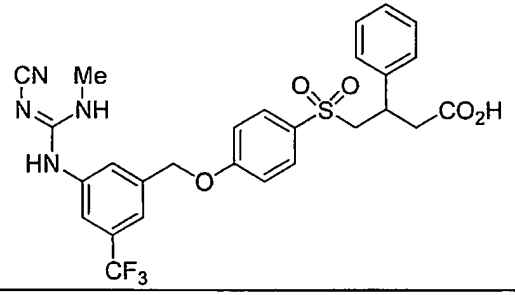
7		120	0.33	5% MeOH / 95% CH_2Cl_2	511 (M+H)+ [HPLC ES-MS]	a	c
8		90	0.29	5% MeOH / 95% CH_2Cl_2	547 (M+H)+ [HPLC ES-MS]	a	
9		115-125	0.32	10% MeOH / 90% CH_2Cl_2	512 (M+H)+ [HPLC ES-MS]	a	
10		155-160	0.54	70% EtOAc / 30% Hexane	527 (M+H)+ [HPLC ES-MS]	b	

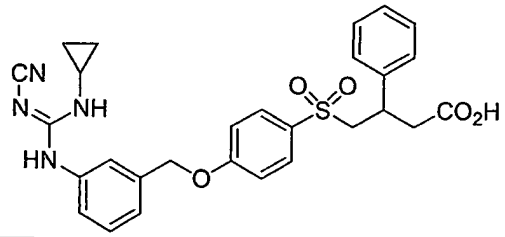
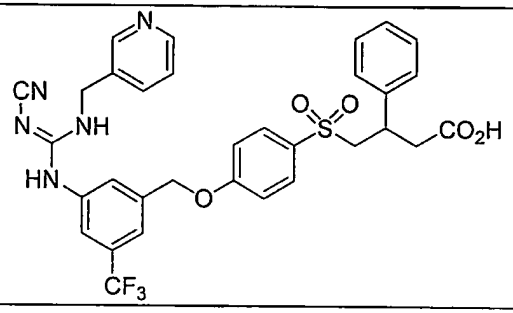
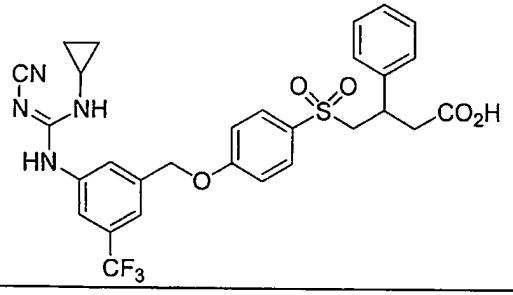
11		60-62	0.29	0.5% AcOH / 5% MeOH / 95.5% CH_2Cl_2	580 $(M+H)^+$ [HPLC ES-MS]	b	
12			0.22	100% EtOAc	509 $(M+H)^+$ [HPLC ES-MS]	b	
13			0.23	0.5% AcOH / 95% MeOH / 94.5% CH_2Cl_2	550 $(M+H)^+$ [HPLC ES-MS]	b	

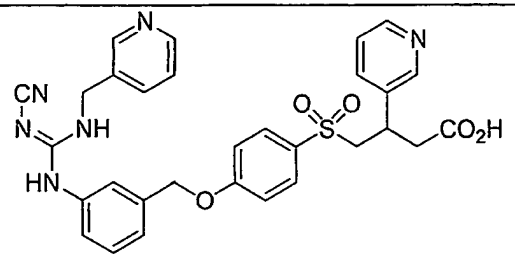
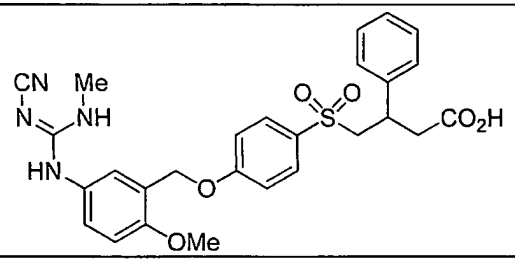
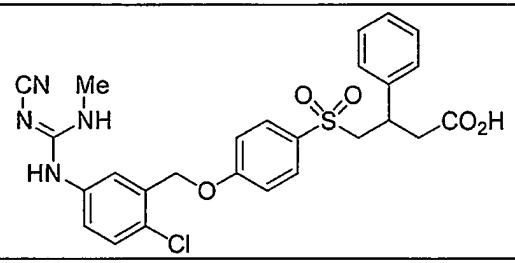
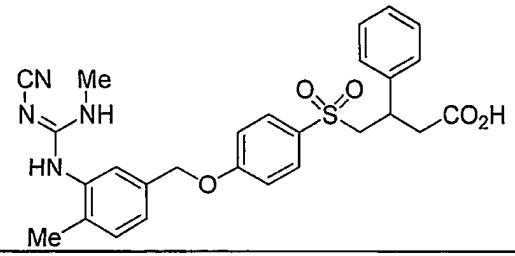
14		203-206 (dec)	0.65	100% EtOAc		b	c
15		175-180 (dec)	0.64	100% EtOAc	501 (M+H)+ [HPLC ES-MS]	b	
16		210-212	0.38	5% MeOH / 95% CH_2Cl_2	617 (M+H)+ [HPLC ES-MS]	c	c

17			0.60	10% MeOH / 90% CH_2Cl_2	577 (M+) [EI]	c
18	diastereomer a		0.01	100% EtOAc		a
19	diastereomer b		0.02	100% EtOAc		a

20			0.50	15% MeOH / 85% CH_2Cl_2		b	
21			0.52	15% MeOH / 85% CH_2Cl_2		b	
22			0.22	10% EtOAc / 90% Hexane		c	

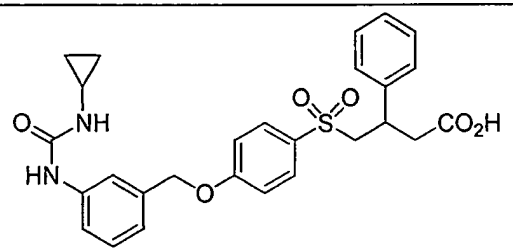
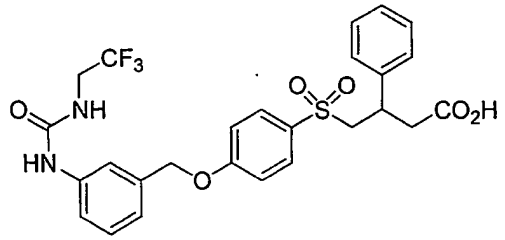
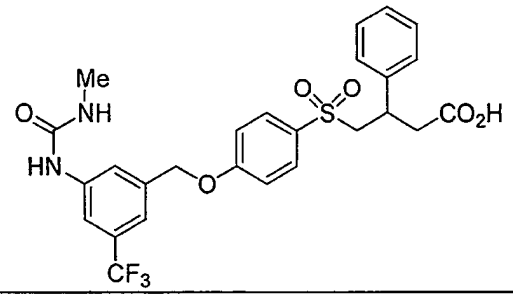
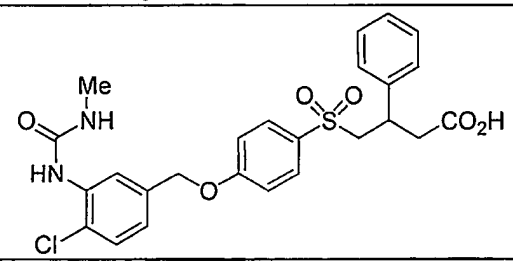
23		103-106	0.44	0.05% AcOH / 1% MeOH / 98.95% CH_2Cl_2	576 (M+H)+ [HPLC ES-MS]	a	
24			0.16	0.1% AcOH / 5% MeOH / 94.9% CH_2Cl_2	508 (M+H)+ [HPLC ES-MS]	a	c
25		255 (dec)	0.61	10% MeOH / 90% EtOAc		a	

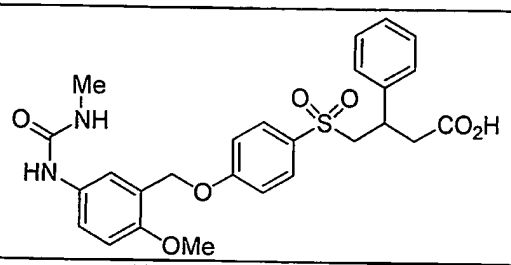
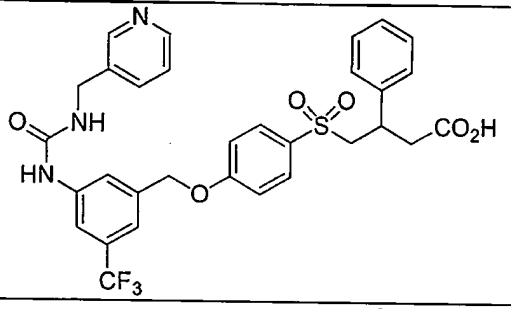
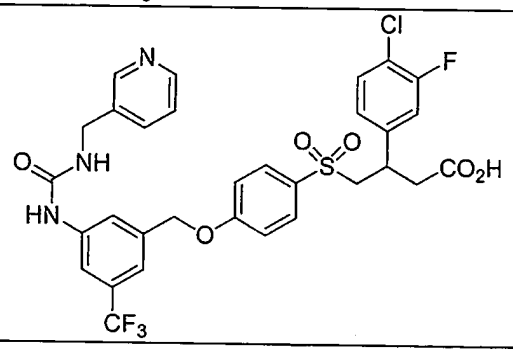
26		210	0.38	15% MeOH / 85% EtOAc	533 (M+) [EI]	b	
27		235 (dec)	0.25	10% MeOH / 90% EtOAc		b	
28		225-230 (dec)	0.63	10% MeOH / 90% EtOAc		b	

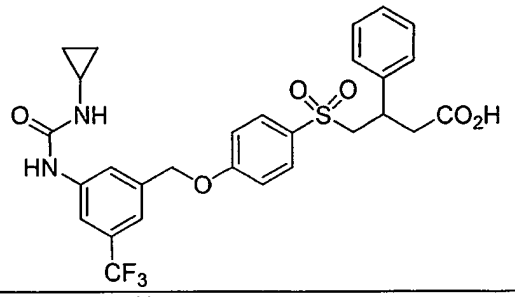
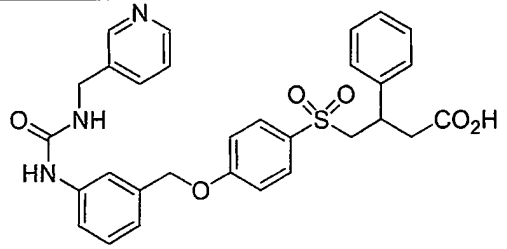
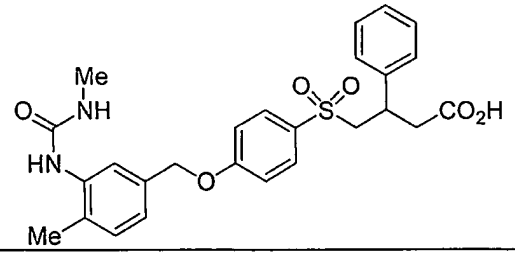
29			0.22	5% MeOH / 95% CH_2Cl_2	585 (M+H)+ [HPLC ES-MS]	b	
30			0.52	10% MeOH / 90% EtOAc	537 (M+H)+ [HPLC ES-MS]	b	
31			0.37	10% MeOH / 90% EtOAc	541 (M+) [EI]	c	
32			0.38	10% MeOH / 90% EtOAc		c	

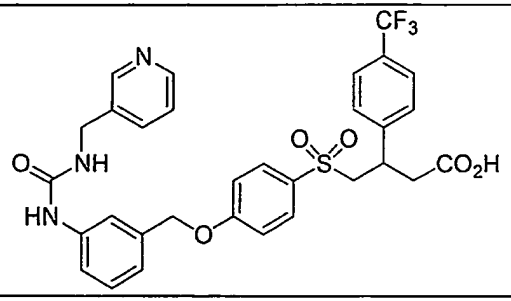
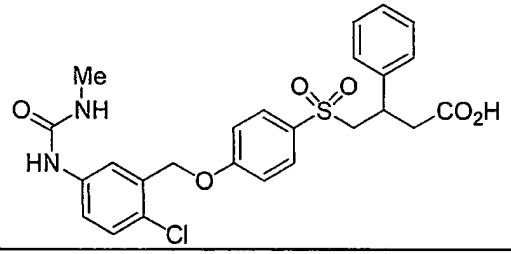
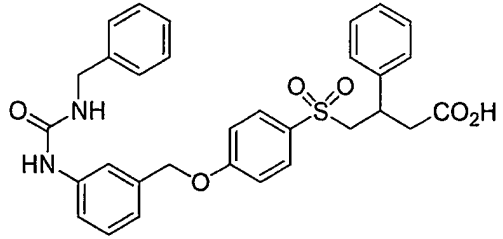
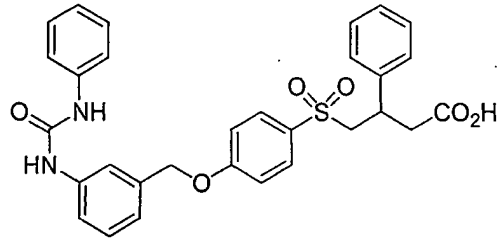
33		161-170		562 (M+H)+ [HPLC ES-MS]	a	c
34		205-210	0.61	576 (M+H)+ [HPLC ES-MS]	b	
35		154-157	0.32	515 (M+) [EI]	a	

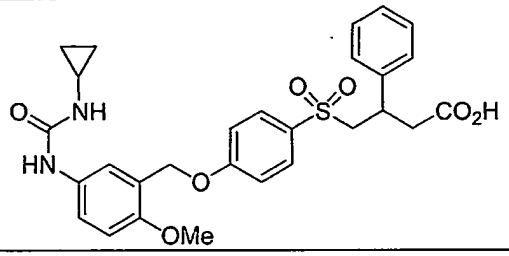
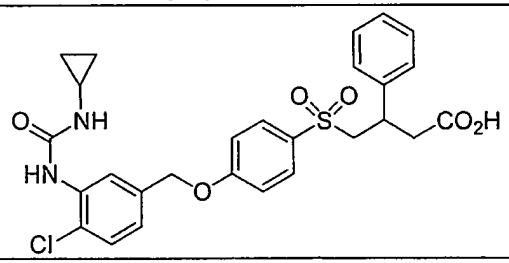
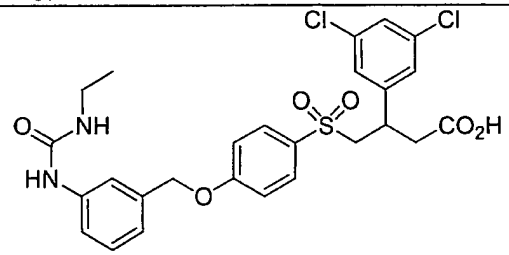
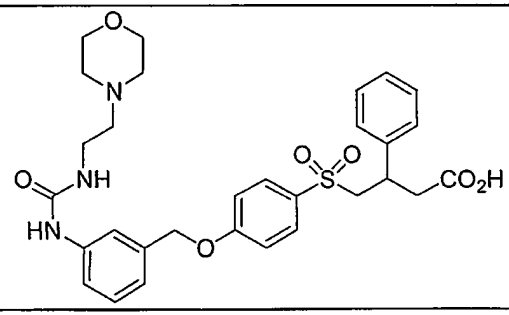
36		165-175	0.45	0.05% AcOH / 1% MeOH / 98.95% CH_2Cl_2	498 (M+H)+ [HPLC ES-MS]	a
37		190-192	0.27	0.5% AcOH / 20% MeOH / 79.5% EtOAc	579 (M+H)+ [HPLC ES-MS]	a
38		188-191	0.54	10% MeOH / 90% CH_2Cl_2	501 (M+H)+ [HPLC ES-MS]	b
39		260 (dec)	0.25	0.1% AcOH / 6% MeOH / CH_2Cl_2	561 (M+H)+ [HPLC ES-MS]	b

40		185-190			500 (M+) [EI]	b	
41		160-165	0.45	100% EtOAc	551 (M+H)+ [HPLC ES-MS]	b	
42		220-225	0.57	12% MeOH / 88% EtOAc	551 (M+H)+ [HPLC ES-MS]	b	
43		190-195	0.60	15% MeOH / 85% EtOAc	517 (M+) [EI]	b	

44		171-175	0.39	15% MeOH / 85% EtOAc	513 (M+H)+ [HPLC ES-MS]	b	
45		191-195	0.24	12% MeOH / 88% EtOAc	628 (M+H)+ [HPLC ES-MS]	b	
46		128	0.30	10% MeOH / 90% CH_2Cl_2	612 (M+) [EI]	b	

47		200 (dec)	0.62	12% MeOH / 88% EtOAc	577 (M+H)+ [HPLC ES-MS]	b	
48		208-210	0.08	25% MeOH / 75% EtOAc	560 (M+) [EI]	b	
49		200-205	0.50	15% MeOH / 85% EtOAc	497 (M+H)+ [HPLC ES-MS]	b	

50		130	0.29	10% MeOH / 90% CH_2Cl_2	628 (M+H)+ [HPLC ES-MS]	c	
51		210-215	0.54	15% MeOH / 85% EtOAc	517 (M+) [EI]	c	
52		174-180	0.25	25% MeOH / 75% EtOAc	559 (M+) [EI]	c	
53		195	0.29	15% MeOH / 85% CH_2Cl_2	545 (M+) [EI]	c	

54		130-135	0.56	15% MeOH / 85% EtOAc	539 (M+H)+ [HPLC ES-MS]	c	
55		190-200	0.65	15% MeOH / 85% EtOAc	543 (M+) [EI]	c	
56		185-188	0.42	10% MeOH / 90% CH_2Cl_2	565 (M+) [EI]	c	
57		140-144	0.08	25% MeOH / 75% EtOAc	583 (M+) [EI]	c	

58		190-200	0.55	15% MeOH / 85% EtOAc	523 (M+H)+ [HPLC ES-MS]	c	j
59		182-185	0.37	10% MeOH / 90% CH_2Cl_2	579 (M+) [EI]	c	j
60			0.42	10% MeOH / 90% CH_2Cl_2		b	j

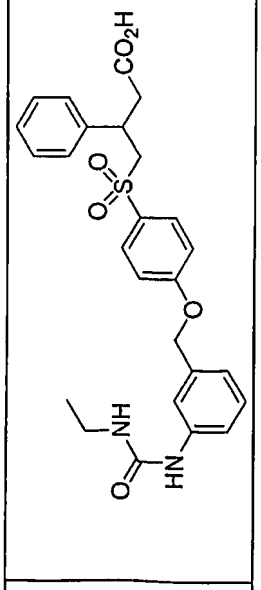
61			0.24	10% MeOH / 90% $CHCl_3$		c

Table 2.

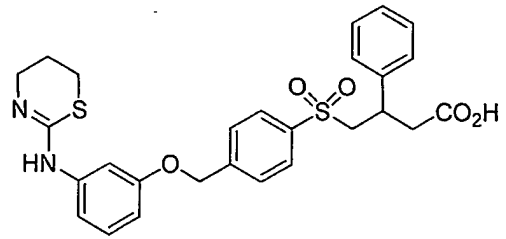
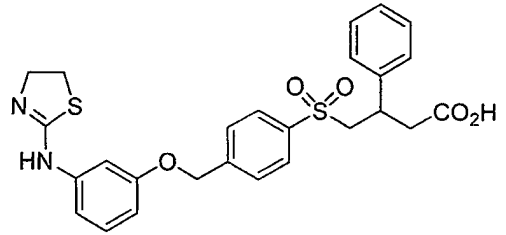
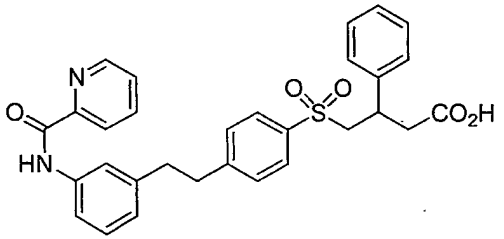
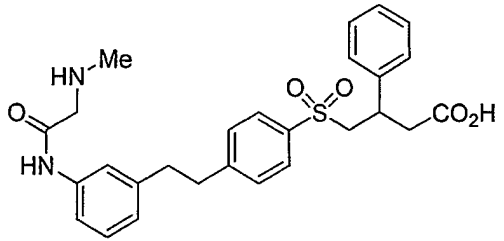
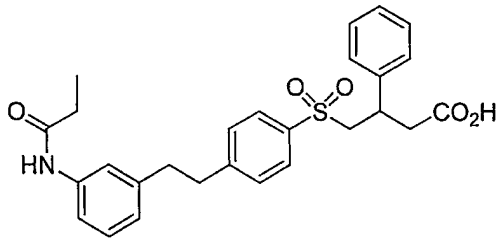
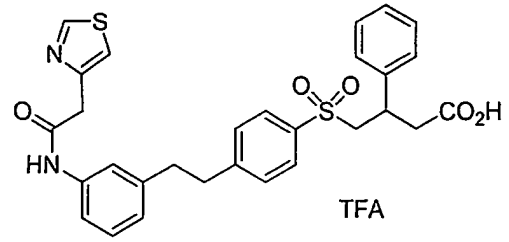
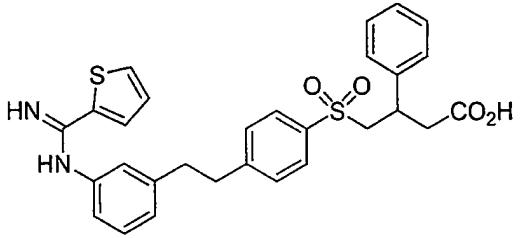
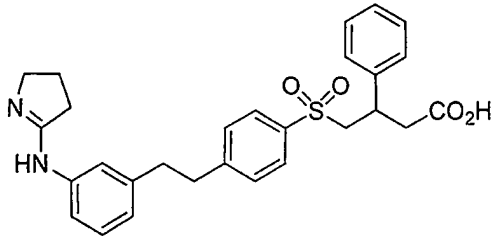
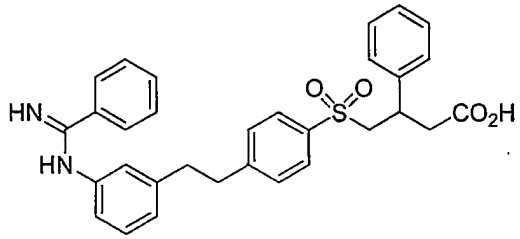
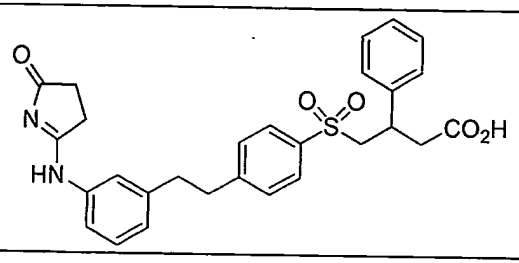
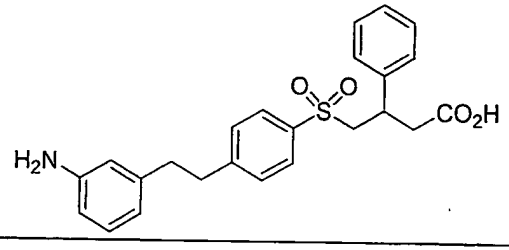
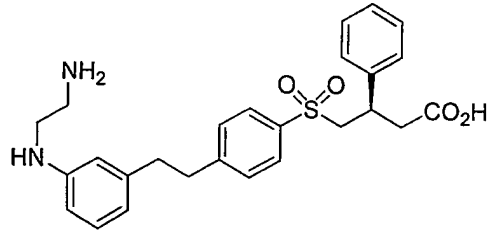
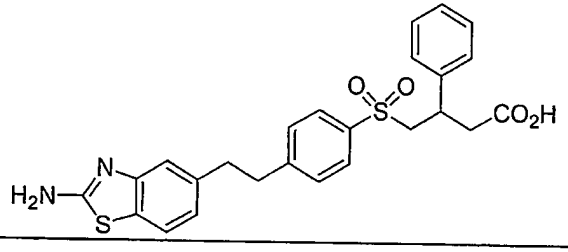
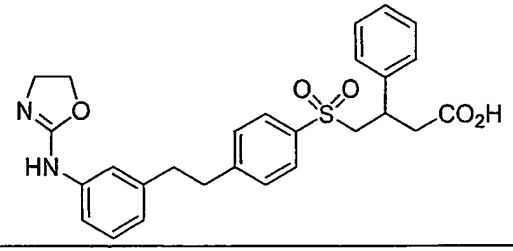
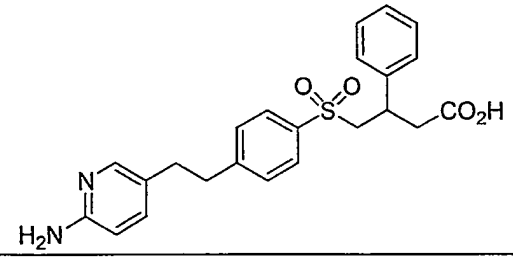
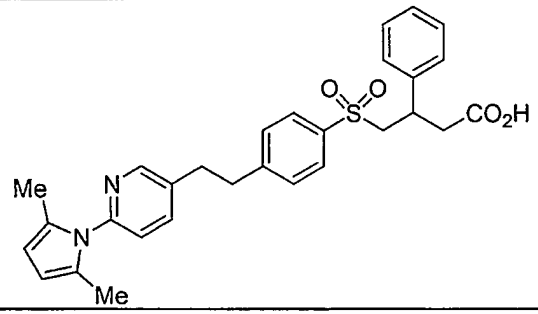
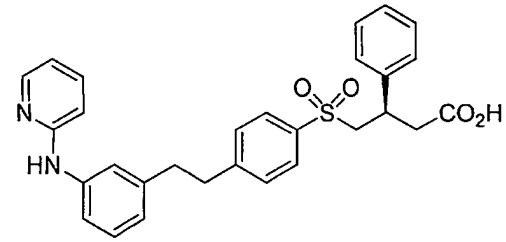
Ex. #	Butyric Acid	mp (°C)	TLC R_f	Solvent System	Mass Spec.	$\alpha_v\beta_3$ IC_{50}	$\alpha_v\beta_5$ IC_{50}
62		181 (dec)	0.42	5% MeOH / 95% CH_2Cl_2	525 (M+) [EI]	a	
63		232 (dec)	0.48	5% MeOH / 95% CH_2Cl_2	511 (M+H)+ [HPLC ES-MS]	b	

Table 3.

Ex.	Butyric Acid	mp (°C)	TLC R_f	Solvent System	Mass Spec.	$\alpha_v\beta_3$ IC_{50}	$\alpha_v\beta_5$ IC_{50}
64			0.22	100% EtOAc		a	
65			0.65	100% MeOH		c	
66			0.62	20% MeOH / 80% Hexane		c	

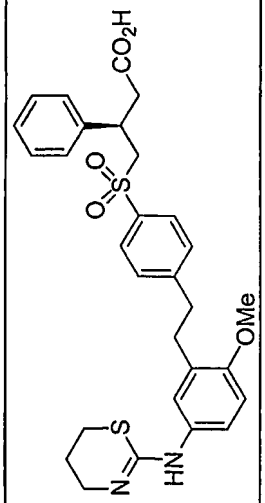
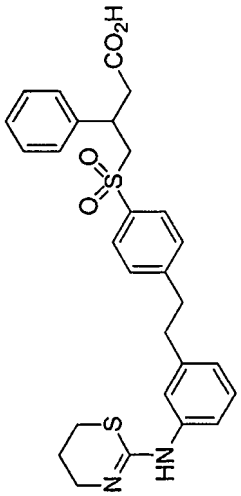
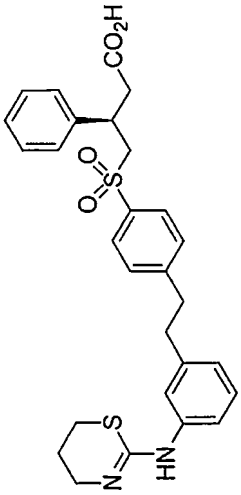
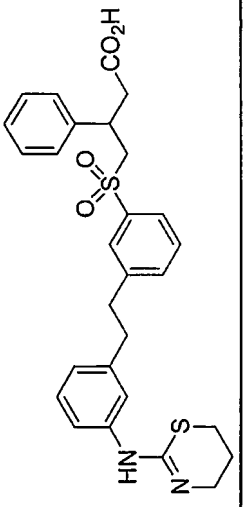
67	 TFA					c	
68			0.74	20% MeOH / 80% $CHCl_3$		a	
69			0.28	40% MeOH / 60% EtOAc		a	c
70			0.63	100% EtOAc		b	

71			0.68	50% MeOH / 50% EtOAc		c	
72			0.45	15% MeOH / 85% EtOAc		b	
73			0.22	30% MeOH / 70% EtOAc		c	
74			0.55	20% MeOH / 80% EtOAc		b	

75			0.10	90% MeOH / 10% CH2CL2	493 (M+H)+ [HPLC ES-MS]	a	
76			0.50	20% MeOH / 80% CH_2Cl_2	425 (M+H)+ [HPLC ES-MS]	b	
77		68-75	0.61	10% MeOH / 90% EtOAc	503 (M+H)+ [HPLC ES-MS]	c	
78			0.50	7% MeOH / 93% CH_2Cl_2		b	

79			0.39	10% MeOH / 90% CH_2Cl_2		c
80	racemic		0.72	10% MeOH / 90% CH_2Cl_2	541 $(M+H)^+$ [HPLC ES-MS]	a
81	enantiomer a	139-140	0.39	10% MeOH / 90% CH_2Cl_2	541 $(M+H)^+$ [HPLC ES-MS]	b

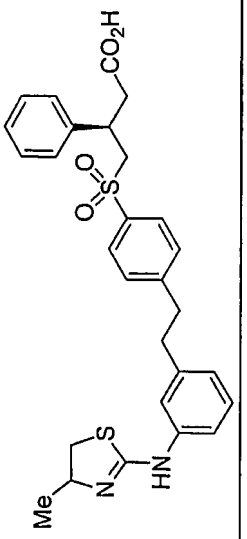
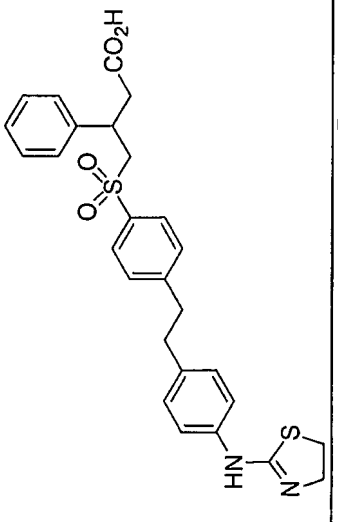
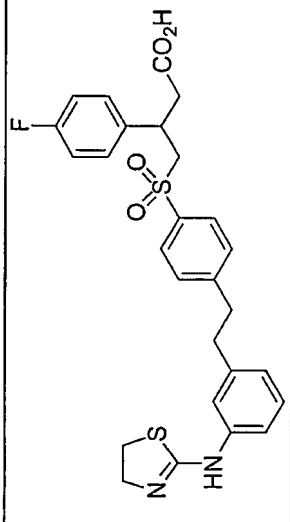
82	enantiomer b	139-140	0.39	10% MeOH / 90% CH_2Cl_2	541 (M+H)+ [HPLC ES-MS]	b
83			0.35	5% MeOH / 95% CH_2Cl_2	541 (M+H)+ [HPLC ES-MS]	b
84		136-140	0.35	10% MeOH / 90% CH_2Cl_2	575 (M+H)+ [HPLC ES-MS]	a

85		208-211	0.48	5% MeOH / 95% CH_2Cl_2	555 (M+) [EI]	b
86			0.20	100% EtOAc		a
87			0.51	10% MeOH / 90% CH_2Cl_2		c
88			0.85	20% MeOH / 80% CH_2Cl_2		a

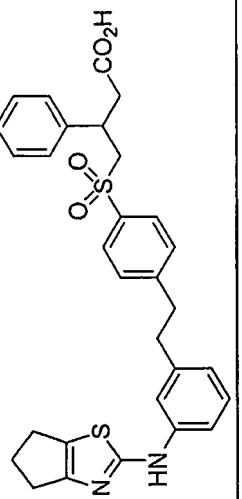
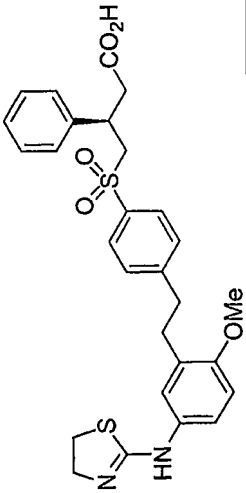
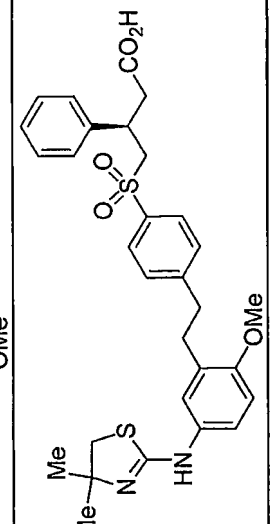
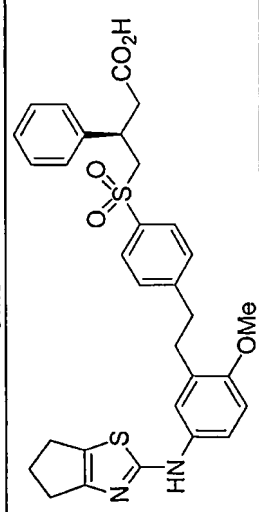
b
b

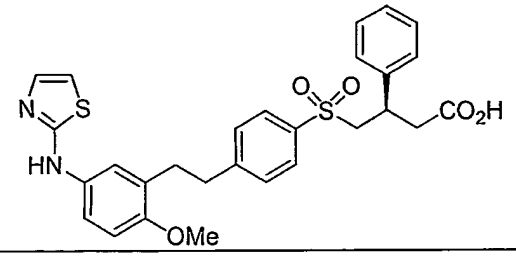
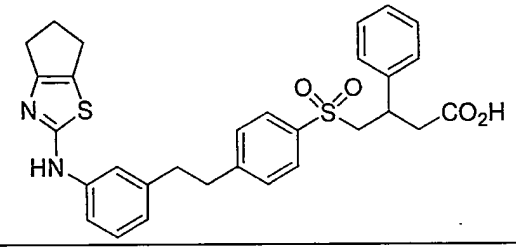
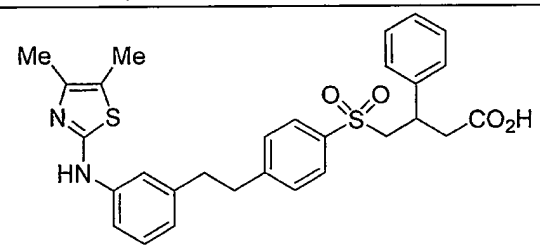
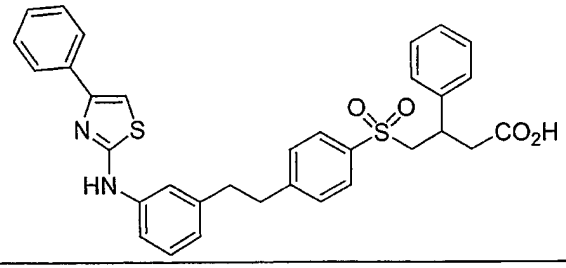
89			0.68	20% MeOH / 80% CH_2Cl_2	a	
90			0.41	20% MeOH / 80% CH_2Cl_2	c	
91			0.22	100% EtOAc	a	c

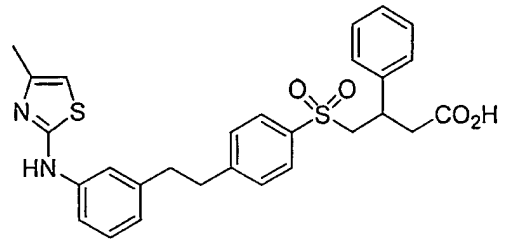
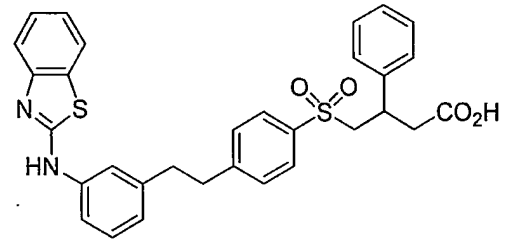
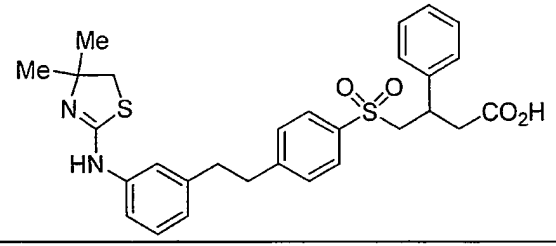
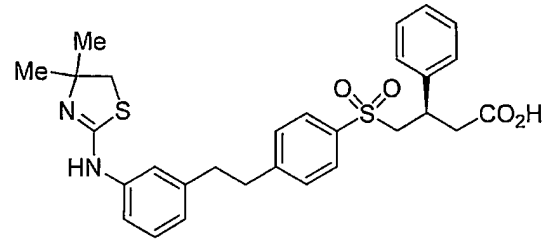
92			0.44	10% MeOH / 90% CH_2Cl_2		c	
93		103-106	0.41	1% AcOH / 10% MeOH / 89% EtOAc		a	c
94			0.50	100% EtOAc		b	
95			0.50	100% EtOAc		a	

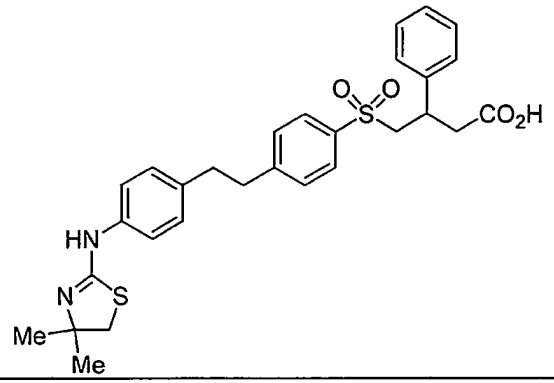
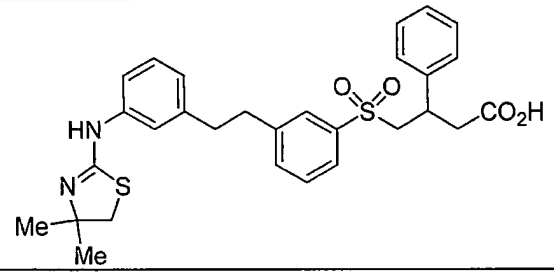
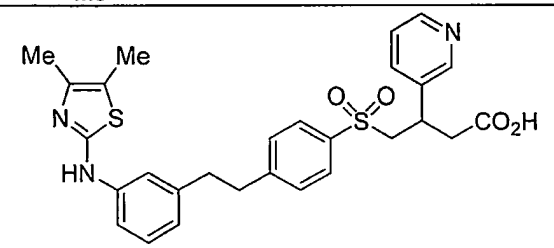
96					b	
97			0.60	10% MeOH / 90% CH_2Cl_2	b	
98		121-124	0.72	10% MeOH / 90% CH_2Cl_2	a	527 (M+H)+ [HPLC ES-MS]

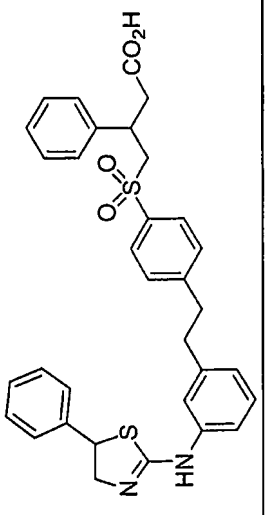
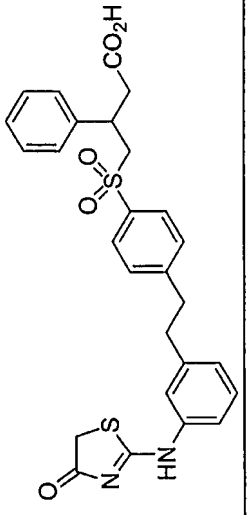
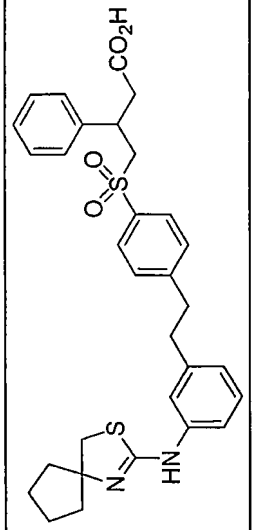
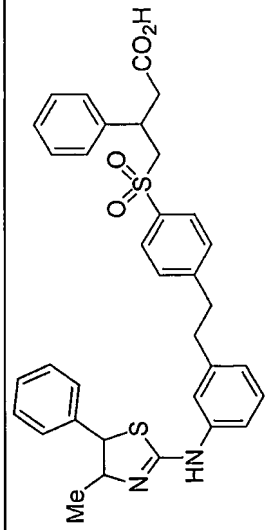
99		135-138	0.50	10% MeOH / 90% CH_2Cl_2	561 (M+) [EI]	b
100			0.28	5% MeOH / 95% CH_2Cl_2	527 (M+H)+ [HPLC ES-MS]	b
101		183-185	0.15	100% EtOAc	525 (M+H)+ [HPLC ES-MS]	c

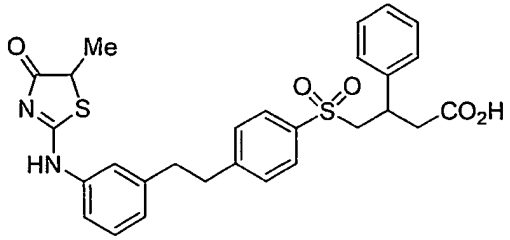
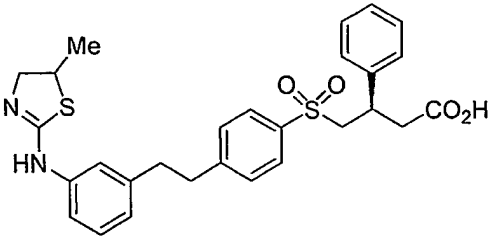
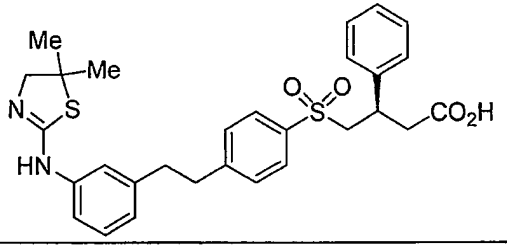
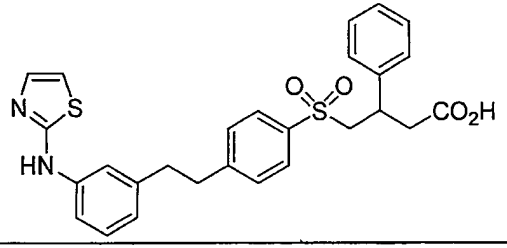
102		98-100	0.20	100% EtOAc	565 $(M+H)^+$ [HPLC ES-MS]	c
103		178-181	0.41	5% MeOH / 95% CH_2Cl_2	539 (M+) [EI]	b
104			0.56	5% MeOH / 95% CH_2Cl_2	567 (M+) [EI]	c
105			0.34	5% MeOH / 95% CH_2Cl_2	577 (M+) [EI]	c

106			0.52	5% MeOH / 95% CH_2Cl_2	537 (M+) [EI]	c	
107			0.40	10% MeOH / 90% EtOAc		a	c
108			0.48	10% MeOH / 90% EtOAc		c	c
109			0.75	10% MeOH / 90% EtOAc		b	

110			0.52	10% MeOH / 90% EtOAc		b	
111			0.75	100% EtOAc		c	
112			0.55	10% MeOH / 90% CH_2Cl_2		b	
113			0.12	5% MeOH / 95% EtOAc		b	

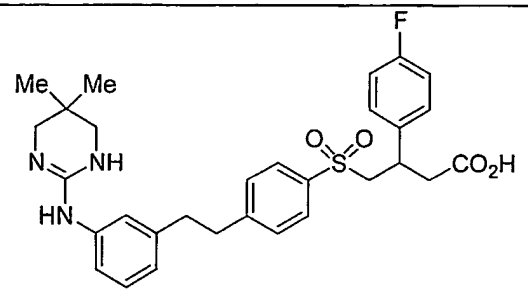
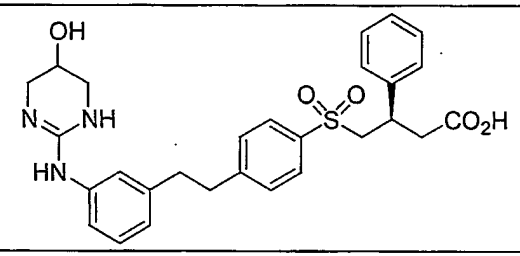
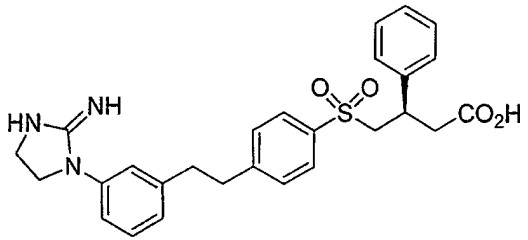
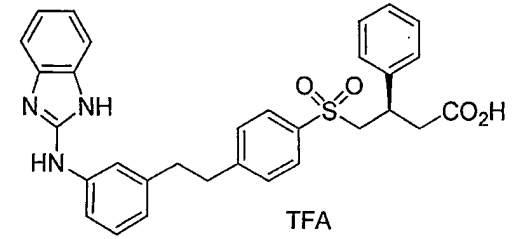
114			0.43	10% MeOH / 90% CH_2Cl_2		b	
115			0.43	10% MeOH / 90% CH_2Cl_2		c	
116			0.68	1% AcOH / 20% MeOH / 79% EtOAc		b	

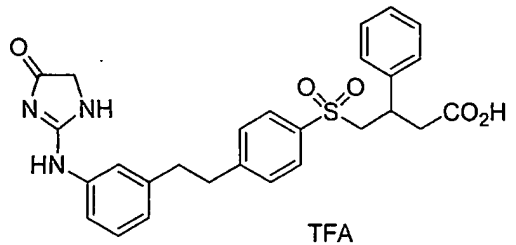
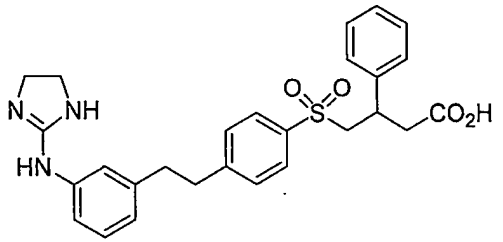
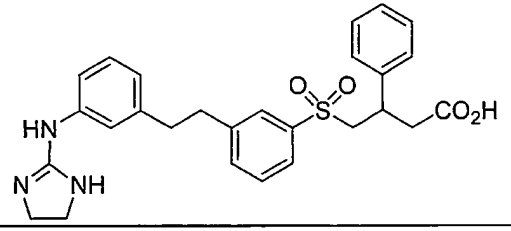
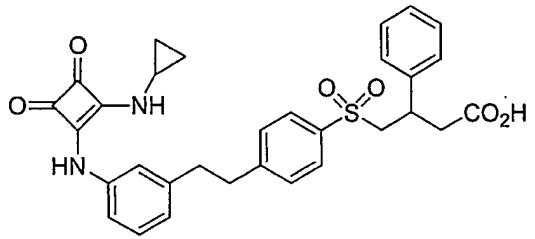
117		0.60	100% EtOAc	b	
118		0.26	10% MeOH / 90% $CHCl_3$	b	
119		0.43	10% MeOH / 90% CH_2Cl_2	c	
120		0.71	20% MeOH / 80% EtOAc	c	

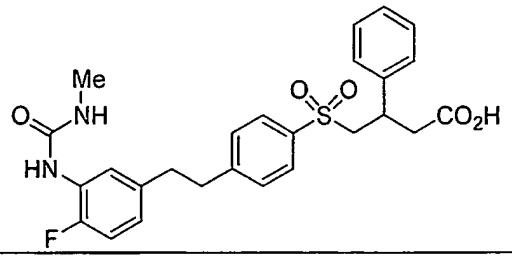
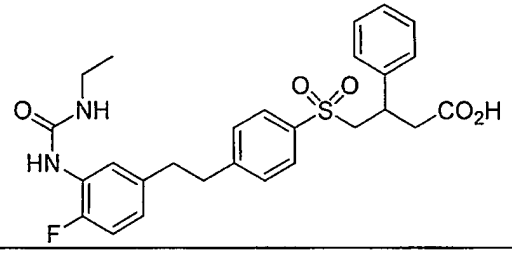
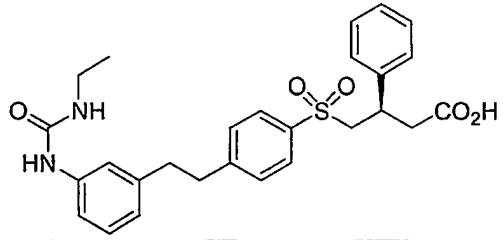
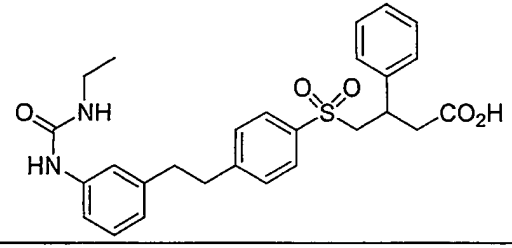
121			0.08	100% EtOAc		c	
122						a	
123			0.70	20% MeOH / 80% EtOAc		b	
124			0.20	10% MeOH / 90% EtOAC	507 (M+H)+ [HPLC ES-MS]	c	c

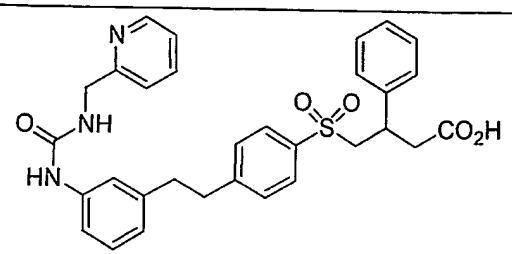
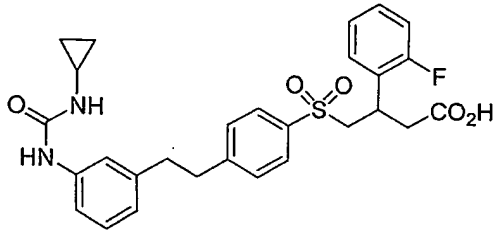
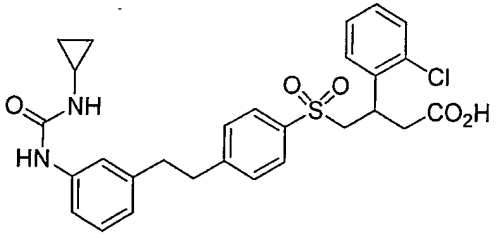
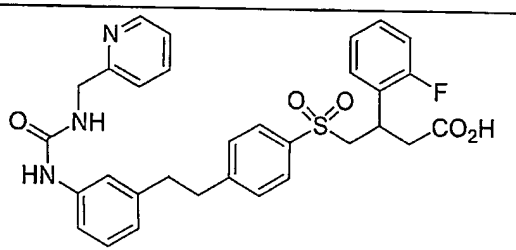
125			0.16	5% MeOH / 95% EtOAc		c
126			0.16	5% MeOH / 95% EtOAc		c
127			0.50	10% MeOH / 90% CH_2Cl_2		c
128			0.30	10% MeOH / 90% CH_2Cl_2	523 (M+H)+ [HPLC ES-MS]	b

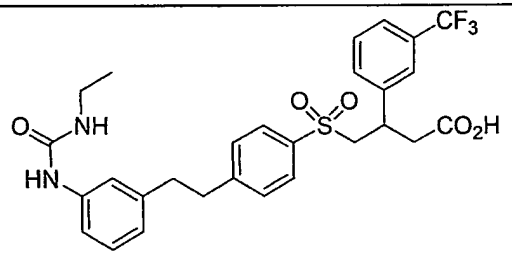
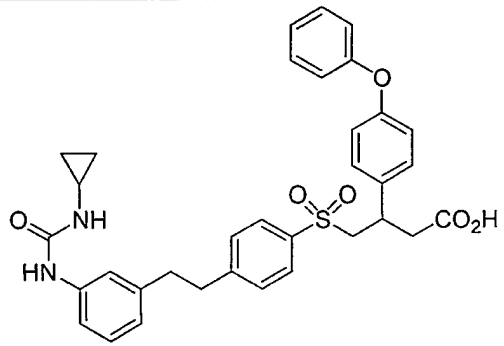
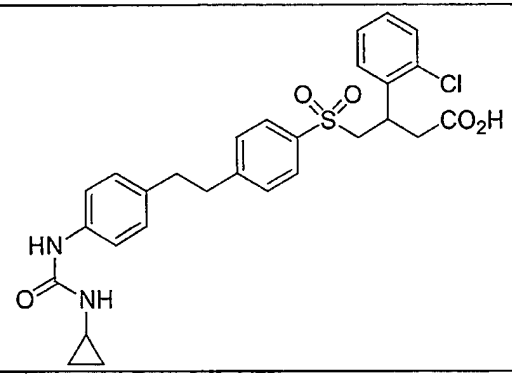
129			0.55	10% MeOH / 90% CH_2Cl_2	524 (M+H)+ [HPLC ES-MS]	a
130			0.25	5% MeOH / 95% CH_2Cl_2	538 (M+H)+ [HPLC ES-MS]	b
131			0.51	10% MeOH / 90% CH_2Cl_2	510 (M+H)+ [HPLC ES-MS]	b

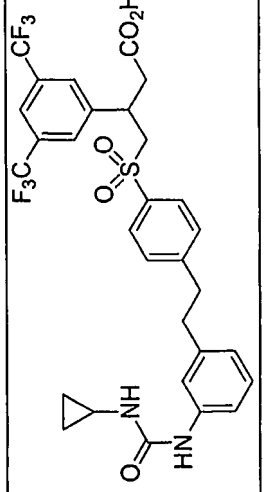
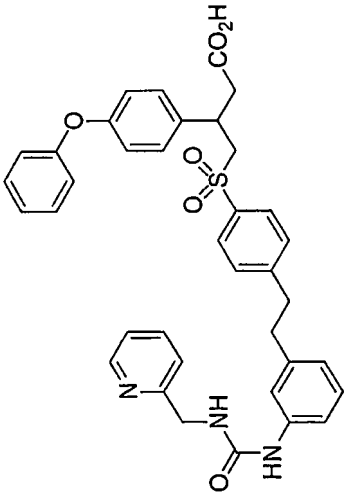
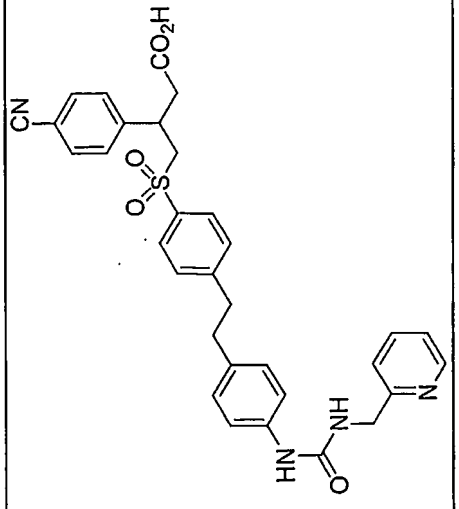
132			0.28	5% MeOH / 95% CH_2Cl_2	552 (M+H)+ [HPLC ES-MS]	b	
133			0.33	20% MeOH / 80% $CHCl_3$		a	
134			0.09	20% MeOH / 80% EtOAc		c	
135	 TFA					c	

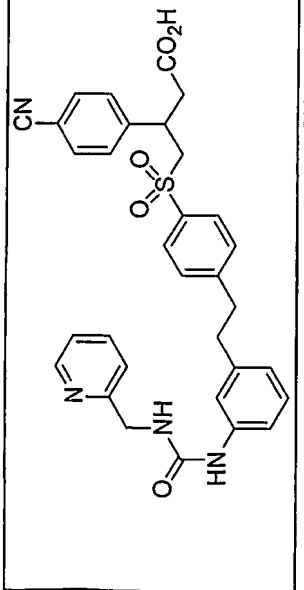
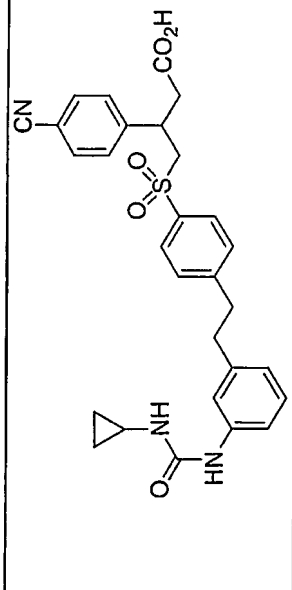
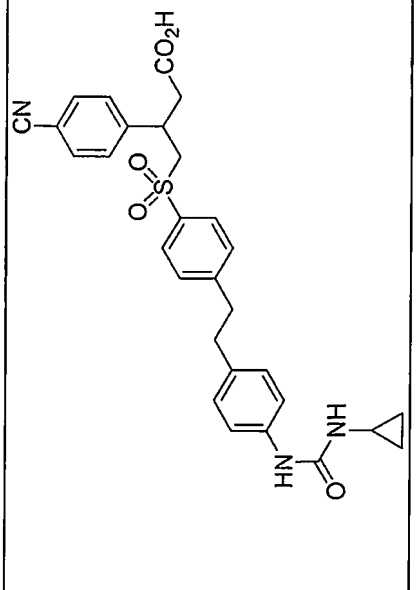
136	 TFA					c	
137			0.40	10% H2O / 90% CH3CN	492 (M+H)+ [HPLC ES-MS]	a	c
138			0.50	20% H2O / 80% CH3CN	492 (M+H)+ [HPLC ES-MS]	a	
139			0.25	25% MeOH / 75% EtOAc		c	

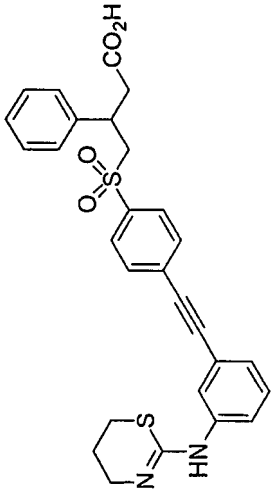
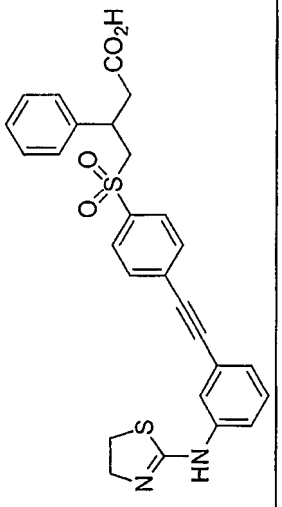
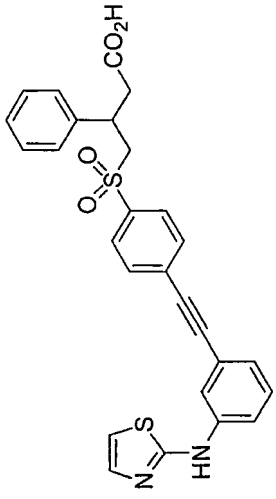
140		145-148	0.54	10% MeOH / 90% CH_2Cl_2	499 (M+H)+ [HPLC ES-MS]	c	
141		79-81	0.58	10% MeOH / 90% CH_2Cl_2	513 (M+H)+ [HPLC ES-MS]	c	
142			0.45	10% MeOH / 90% EtOAc		b	
143			0.23	10% MeOH / 90% EtOAc		b	

144			0.20	10% MeOH / 90% EtOAc		b	
145					525 (M+H)+ [HPLC ES-MS]	b	
146					541 (M+H)+ [HPLC ES-MS]	b	
147					576 (M+H)+ [HPLC ES-MS]	b	

148					563 (M+H)+ [HPLC ES-MS]	b	
149					599 (M+H)+ [HPLC ES-MS]	c	
150					541 (M+H)+ [HPLC ES-MS]	c	

151				643 (M+H)+ [HPLC ES-MS]	c
152				650 (M+H)+ [HPLC ES-MS]	c
153				583 (M+H)+ [HPLC ES-MS]	c

154				583 (M+H)+ [HPLC ES-MS]	c	
155				532 (M+H)+ [HPLC ES-MS]	c	
156				532 (M+H)+ [HPLC ES-MS]	c	

157			0.03	100% EtOAc	b
158			0.46	20% MeOH / $CHCl_3$	c
159			0.67	20% MeOH / 80% $CHCl_3$	b

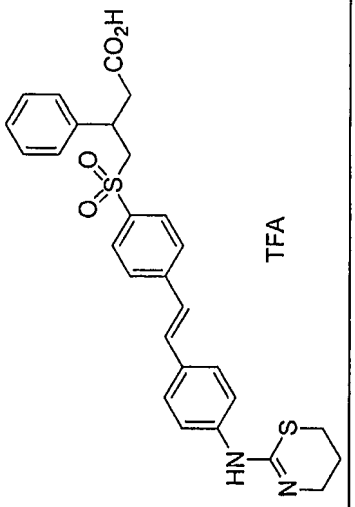
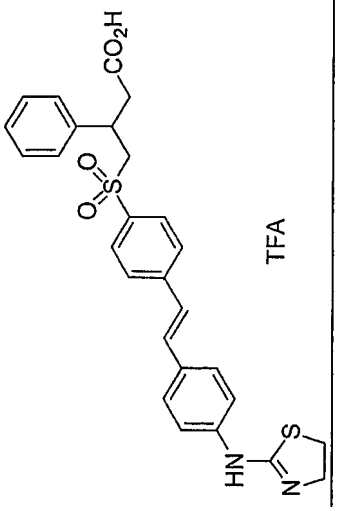
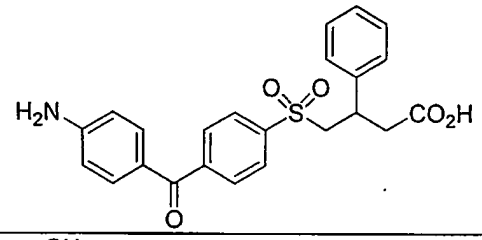
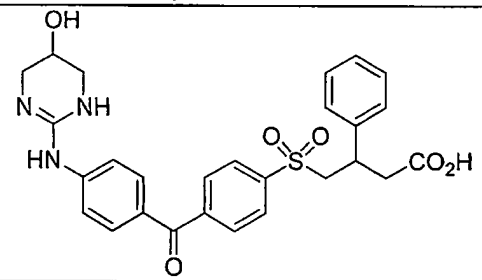
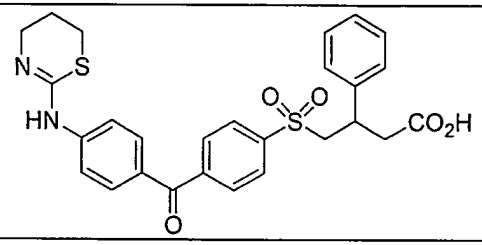
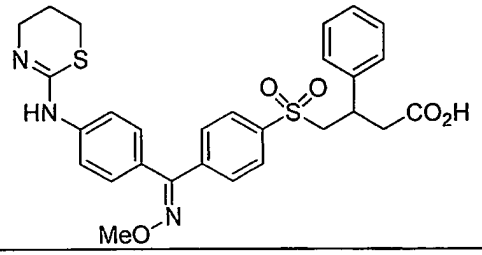
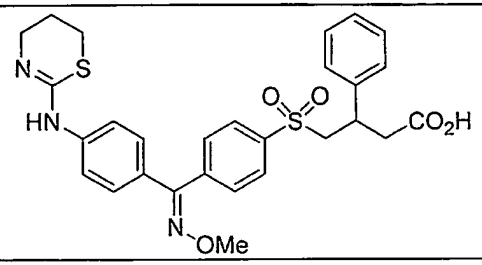
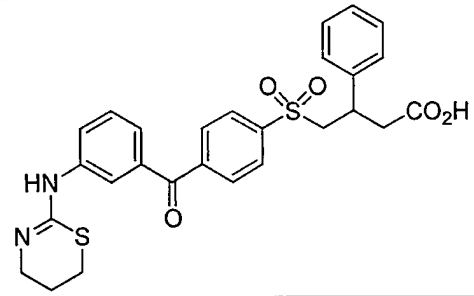
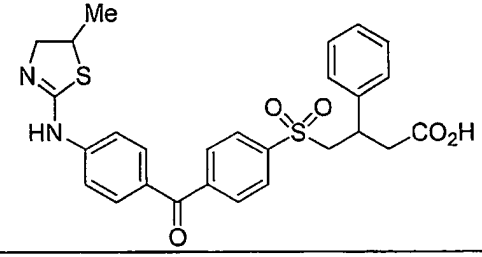
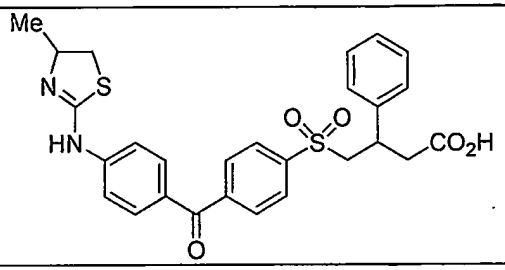
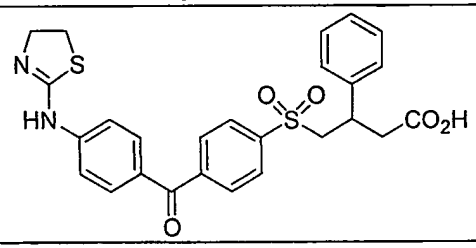
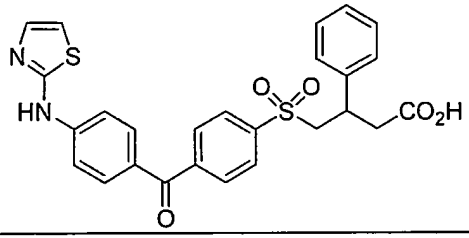
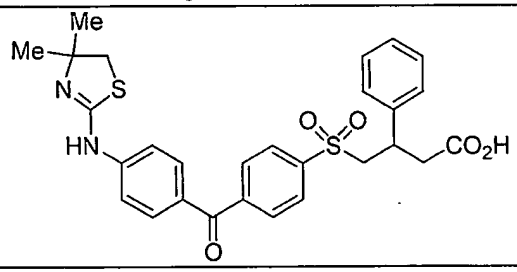
a					
b					
					
					
160					
161					

Table 4.

Ex. #	Butyric Acid	mp (°C)	TLC R_f	Solvent System	Mass Spec.	$\alpha v\beta_3$ IC_{50}	$\alpha v\beta_5$ IC_{50}
162			0.15	10% MeOH / 90% CH_2Cl_2	424 (M+H)+ [HPLC ES-MS]	c	
163			0.10	20% MeOH / 80% CH_2Cl_2	522 (M+H)+ [HPLC ES-MS]	a	
164			0.14	100% EtOAc	523 (M+H)+ [HPLC ES-MS]	a	

165			0.37	9% MeOH / 91% CH_2Cl_2	552 (M+H)+ [HPLC ES-MS]	a	
166			0.34	9% MeOH / 91% CH_2Cl_2	552 (M+H)+ [HPLC ES-MS]	a	
167			0.30	9% MeOH / 91% CH2CL2	523 (M+H)+ [HPLC ES-MS]	b	
168		115-118	0.38	10% MeOH / 90% CH_2Cl_2	523 (M+H)+ [HPLC ES-MS]	a	

169		110-113	0.42	10% MeOH / 90% CH_2Cl_2	523 (M+H)+ [HPLC ES-MS]	a	
170		122-125	0.26	10% MeOH / 90% EtOAc	509 (M+H)+ [HPLC ES-MS]	b	
171			0.18	9% MeOH / 91% CH_2Cl_2	507 (M+H)+ [HPLC ES-MS]	b	
172		120-122	0.43	10% MeOH / 90% CH_2Cl_2	537 (M+H)+ [HPLC ES-MS]	b	

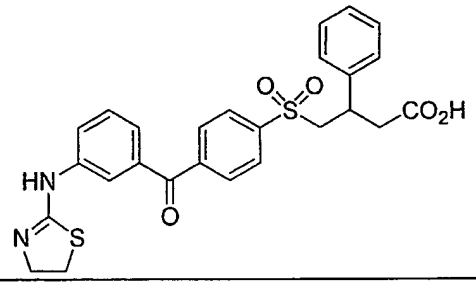
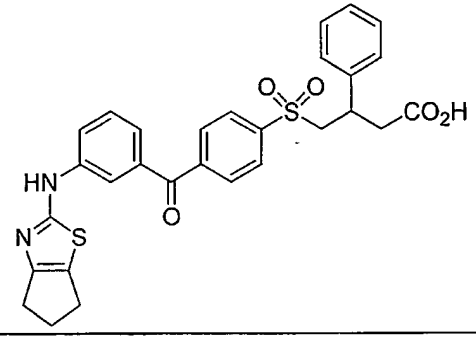
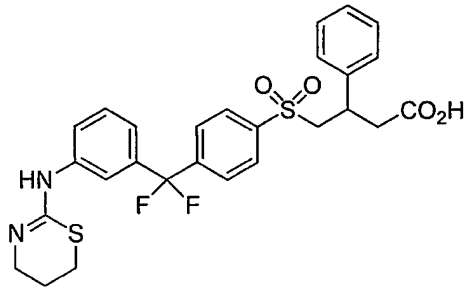
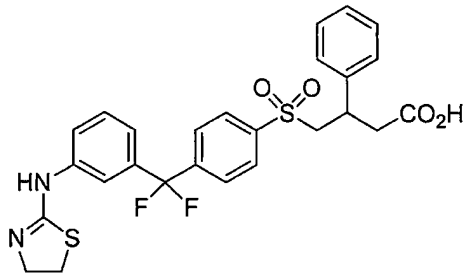
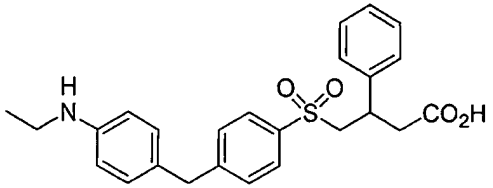
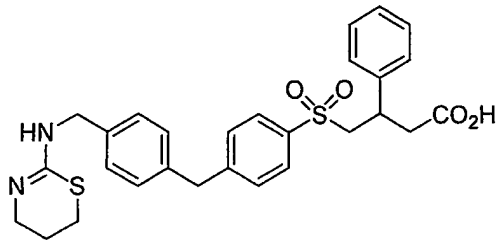
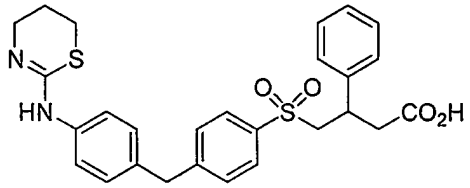
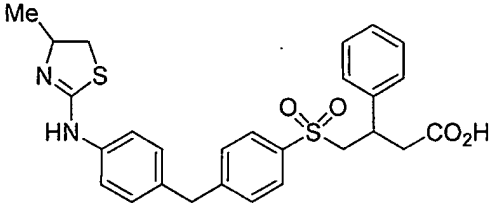
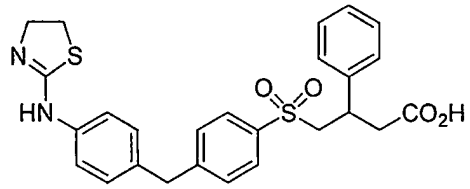
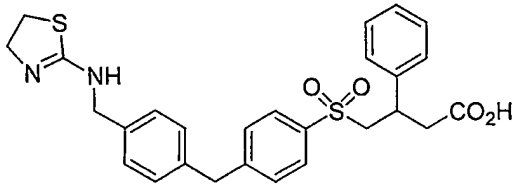
173			0.24	9% MeOH / 91% CH_2Cl_2	547 (M+H)+ [HPLC ES-MS]	b	
174		126-128	0.23	5% MeOH / 95% CH_2Cl_2	547 (M+H)+ [HPLC ES-MS]	c	

Table 5.

Ex. #	Butyric Acid	mp (°C)	TLC R_f	Solvent System	Mass Spec.	$\alpha_V\beta_3$ IC_{50}	$\alpha_V\beta_5$ IC_{50}
175			0.09	10% MeOH / 90% EtOAc	545 (M+H)+ [HPLC ES-MS]	b	
176		185-190	0.10	70% EtOAc / 30% Hexane	531 (M+H)+ [HPLC ES-MS]	b	
177		107-110	0.22	100% EtOAc	438 (M+H)+ [HPLC ES-MS]	c	

178			0.23	10% MeOH / 90% CH_2Cl_2	523 (M+H)+ [HPLC ES-MS]	a	
179		152-155	0.27	9% MeOH / 91% CH_2Cl_2	509 (M+H)+ [HPLC ES-MS]	b	
180		103-107	0.52	20% MeOH / 80% CH_2Cl_2	509 (M+H)+ [HPLC ES-MS]	a	
181		120-124	0.43	9% MeOH / 91% CH_2Cl_2	495 (M+H)+ [HPLC ES-MS]	a	
182			0.19	10% MeOH / 90% CH_2Cl_2	509 (M+H)+ [HPLC ES-MS]	b	

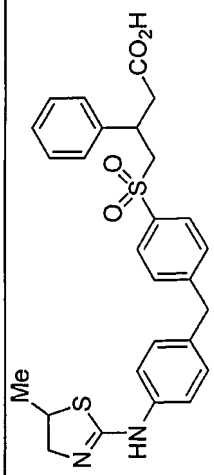
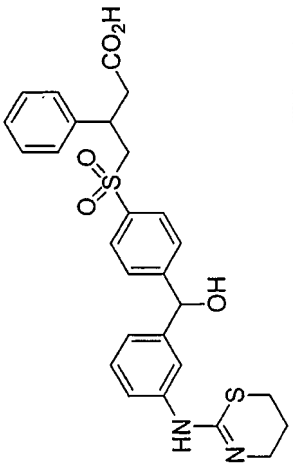
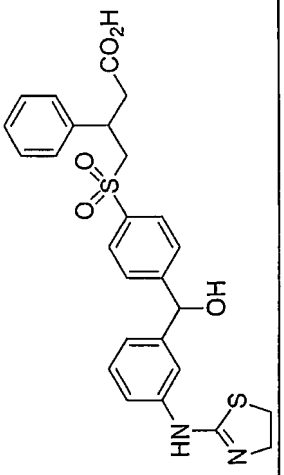
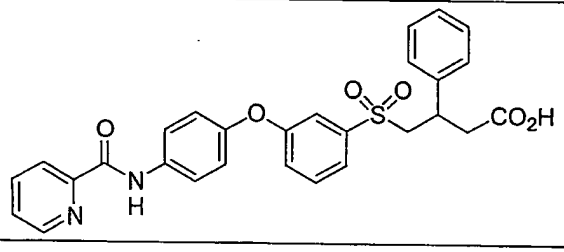
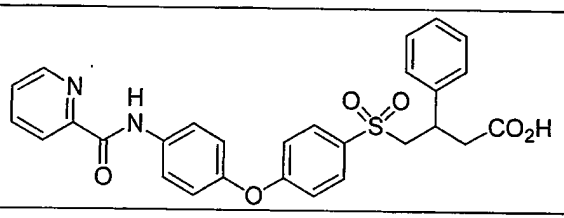
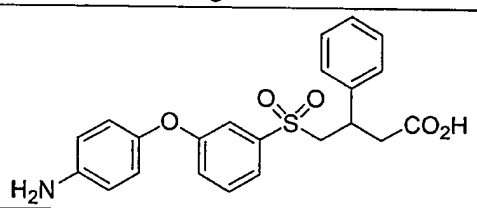
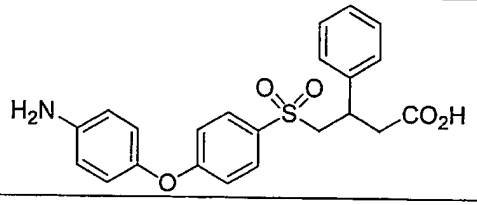
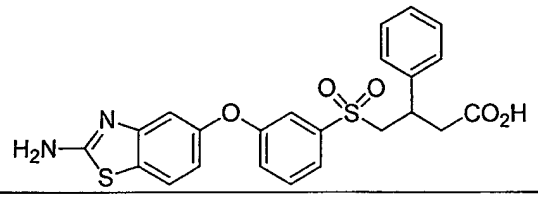
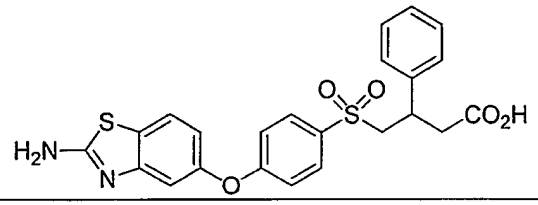
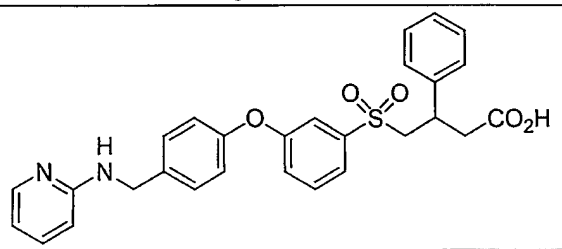
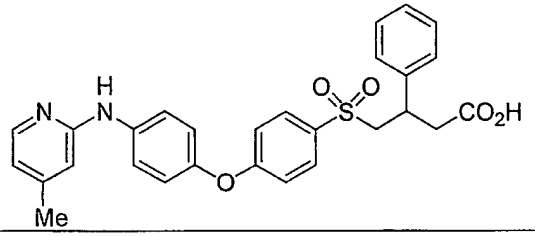
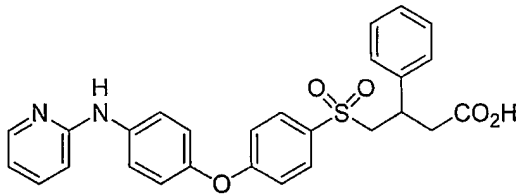
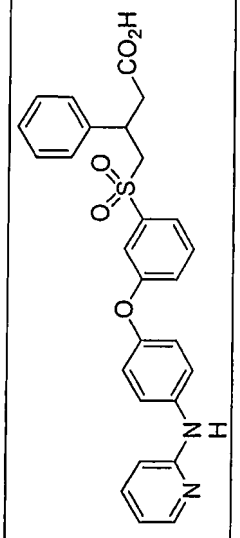
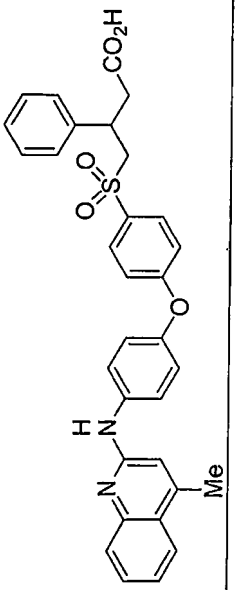
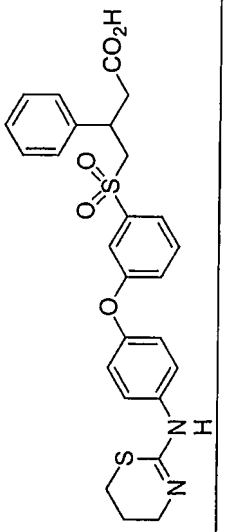
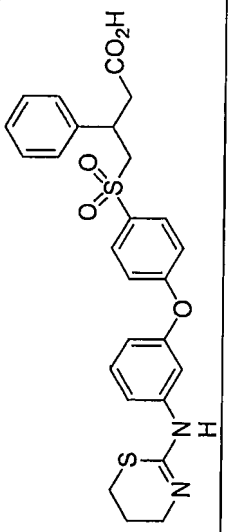
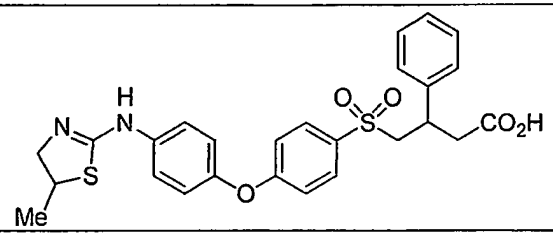
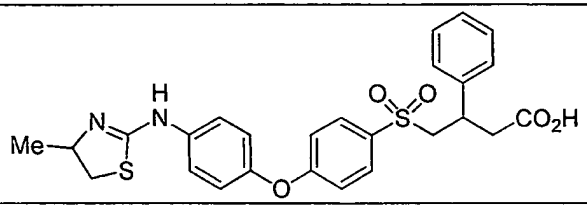
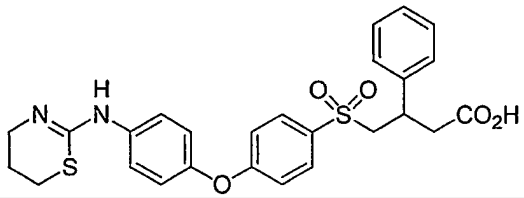
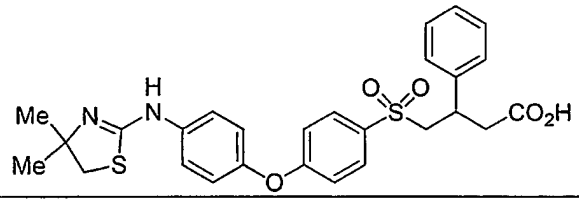
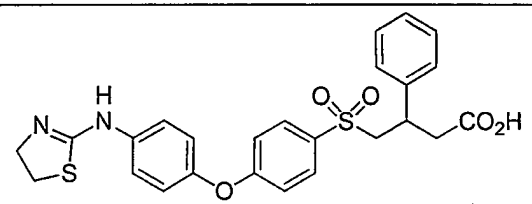
183		102-105	0.50	20% MeOH / 80% CH_2Cl_2	509 $(M+H)^+$ [HPLC ES-MS]	c.
184		143-146	0.19	9% MeOH / 91% CH_2Cl_2	525 $(M+H)^+$ [HPLC ES-MS]	a
185		150-153	0.08	100% EtOAc	511 $(M+H)^+$ [HPLC ES-MS]	a

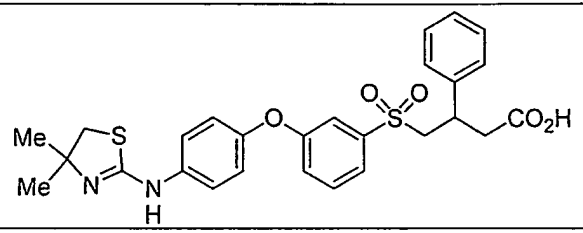
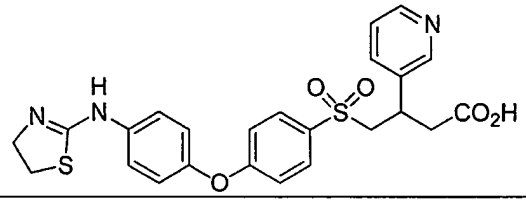
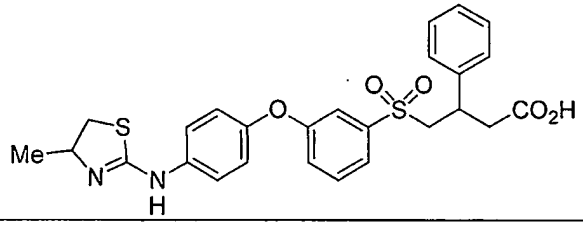
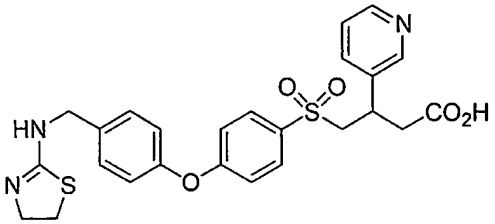
Table 6.

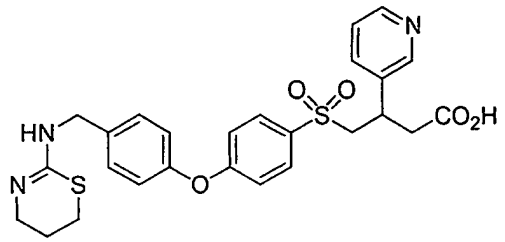
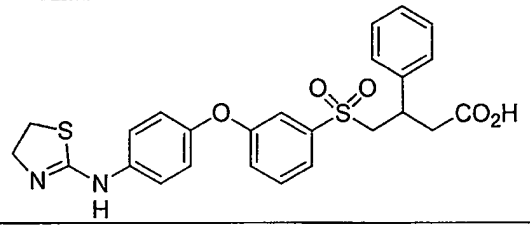
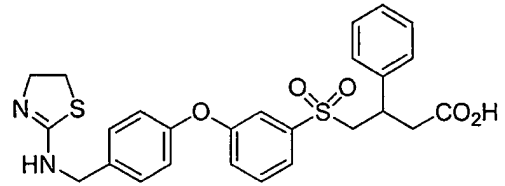
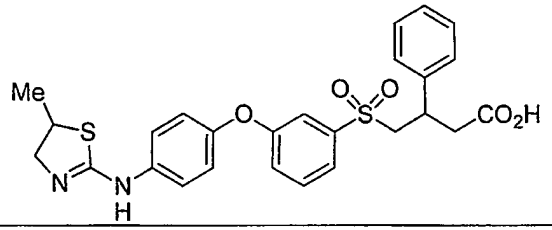
Ex. #	Butyric Acid	mp (°C)	TLC R_f	Solvent System	Mass Spec.	$\alpha_V\beta_3$ IC_{50}	$\alpha_V\beta_5$ IC_{50}
186			0.82	1% AcOH / 10% MeOH / 89% EtOAc		c	
187			0.82	1% AcOH / 10% MeOH / 89% EtOAc		c	
188		79-81	0.58	1% AcOH / 10% MeOH / 89% EtOAc		b	
189		73-76	0.52	1% AcOH / 10% MeOH / 89% EtOAc		c	

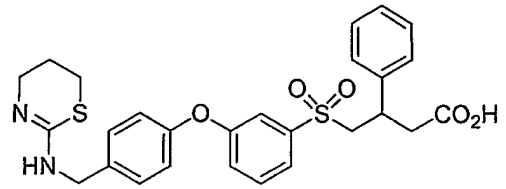
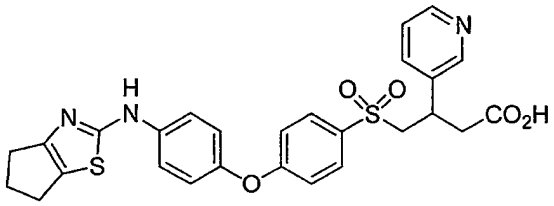
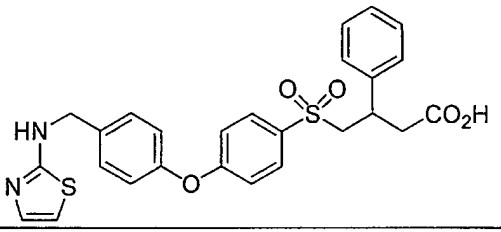
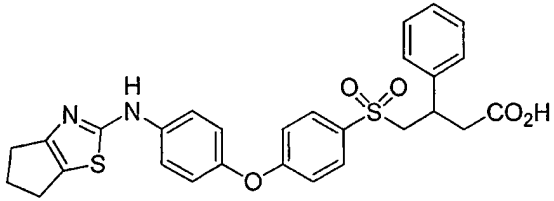
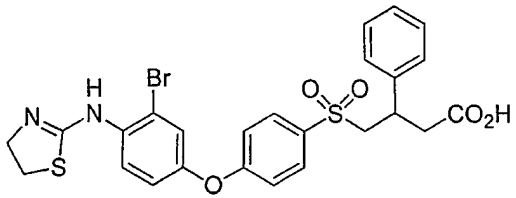
190		88-90	0.18	10% MeOH / 90% CH_2Cl_2	469 (M+H)+ [HPLC ES-MS]	b	
191			0.59	1% AcOH / 10% MeOH / 89% EtOAc	469 (M+H)+ [HPLC ES-MS]	c	
192		94-96	0.56	1% AcOH / 10% MeOH / 89% EtOAc	503 (M+H)+ [HPLC ES-MS]	a	
193		205-207	0.28	100% EtOAc	503 (M+H)+ [HPLC ES-MS]	c	
194		197-199	0.12	10% MeOH / 90% EtOAc		a	

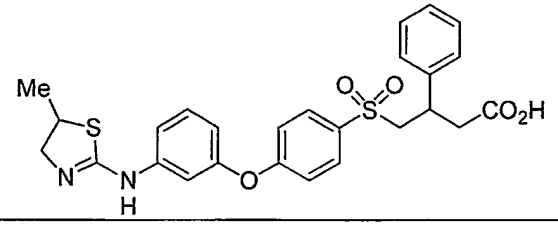
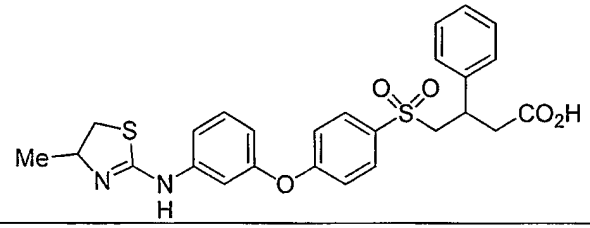
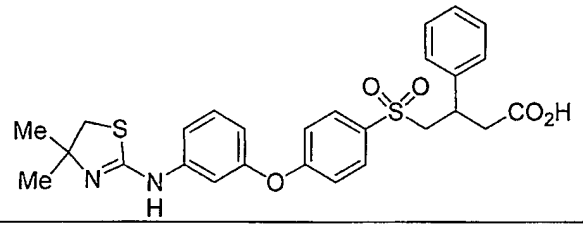
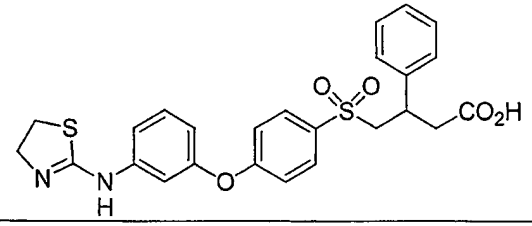
195		92-95	0.66	10% MeOH / 90% EtOAc		b	c
196		194-196	0.63	1% AcOH / 10% MeOH / 89% EtOAc		c	
197		169-171	0.05	1% AcOH / 10% MeOH / 89% EtOAc	511 (M+H)+ [HPLC ES-MS]	a	
198		138-140	0.11	10% MeOH / 90% CH_2Cl_2	511 (M+H)+ [HPLC ES-MS]	b	

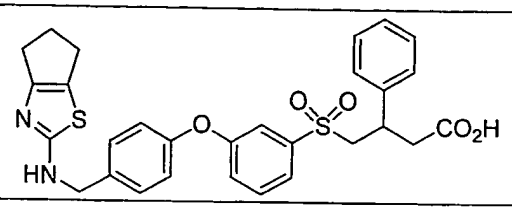
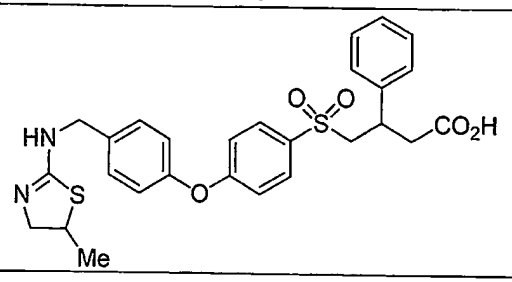
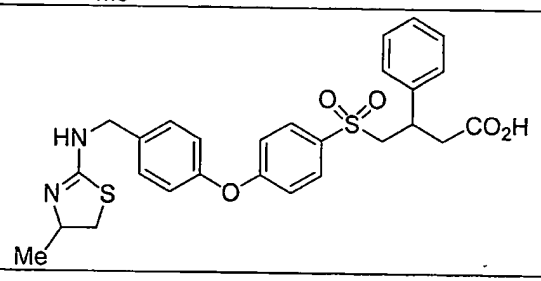
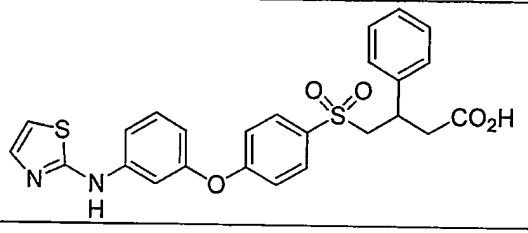
199		122-124	0.21	10% MeOH / 90% CH_2Cl_2	511 (M+H)+ [HPLC ES-MS]	a	c
200		129-133	0.24	10% MeOH / 90% CH_2Cl_2	511 (M+H)+ [HPLC ES-MS]	a	b
201		144-147	0.04	10% MeOH / 90% CH_2Cl_2	511 (M+H)+ [HPLC ES-MS]	a	b
202		145-148	0.15	5% MeOH / 95% CH_2Cl_2	525 (M+H)+ [HPLC ES-MS]	a	
203		186-188	0.61	0.5% AcOH / 10% MeOH / 89.5% EtOAc	497 (M+H)+ [HPLC ES-MS]	a	c

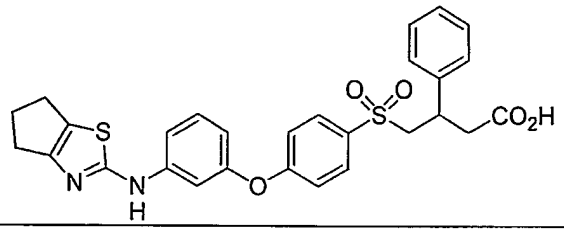
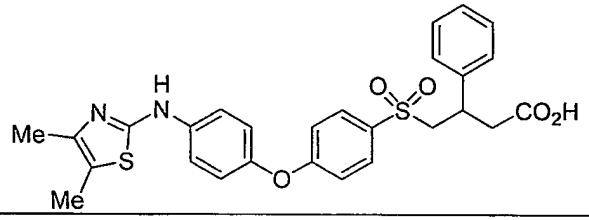
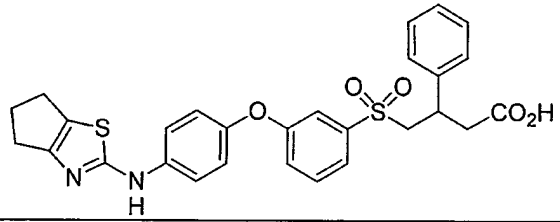
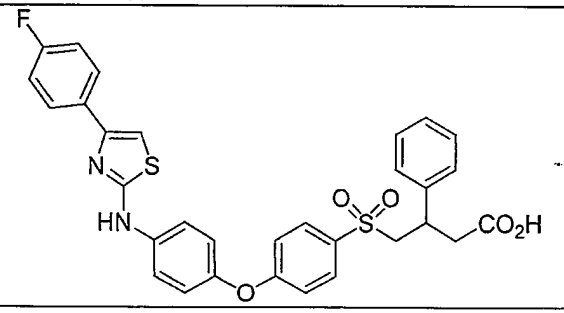
204		185-187 (dec)	0.23	1% AcOH / 10% MeOH / 89% EtOAc	525 (M+H)+ [HPLC ES-MS]	a	
205		129-132	0.35	20% MeOH / 80% CH_2Cl_2	536 (M+H)+ [HPLC ES-MS]	a	b
206		148-150	0.24	1% AcOH / 10% MeOH / 89% EtOAc	511 (M+H)+ [HPLC ES-MS]	a	
207		107-110			511 (M+H)+ [HPLC ES-MS]	a	

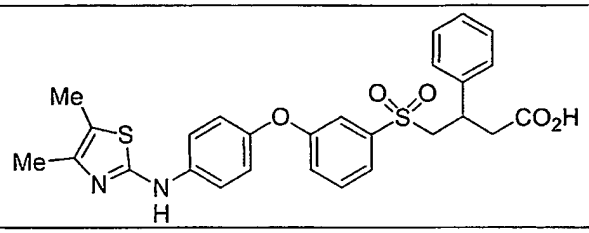
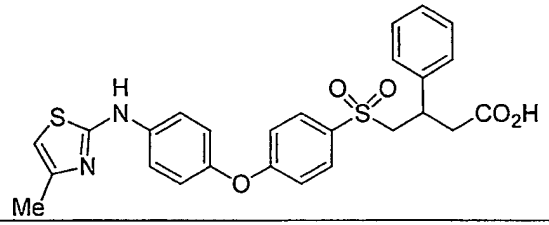
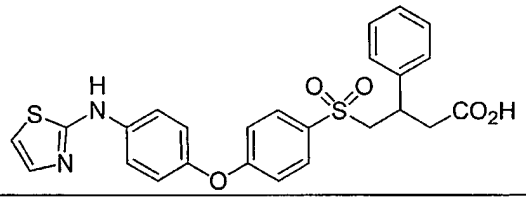
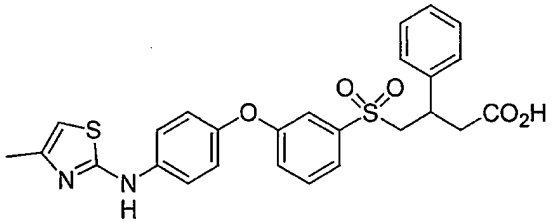
208		183-184 (dec)	0.27	30% MeOH / 70% CH_2Cl_2	525 (M+H)+ [HPLC ES-MS]	a	c
209		160-162	0.17	1% AcOH / 10% MeOH / 89% EtOAc	497 (M+H)+ [HPLC ES-MS]	a	
210		104-106	0.55	10% MeOH / 90% CH_2Cl_2	511 (M+H)+ [HPLC ES-MS]	a	
211		153-155	0.44	1% AcOH / 10% MeOH / 89% EtOAc	511 (M+H)+ [HPLC ES-MS]	a	

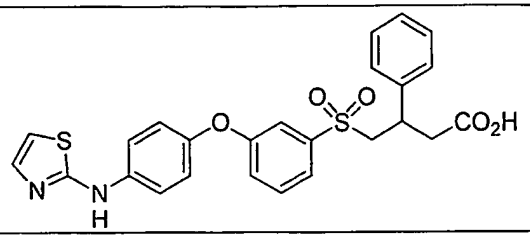
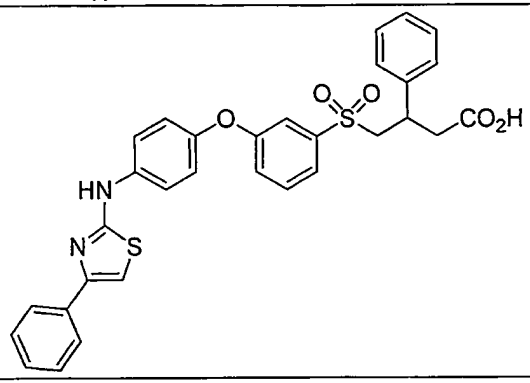
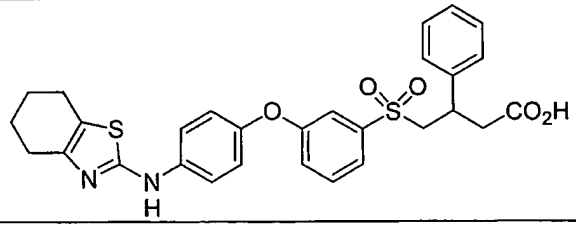
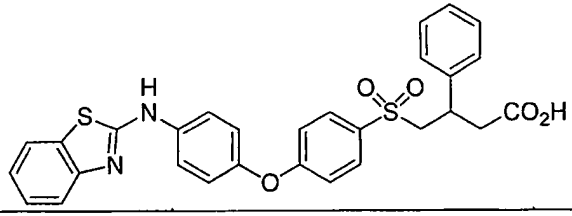
212		128-130	0.37	30% MeOH / 70% CH_2Cl_2	525 (M+H)+ [HPLC ES-MS]	a	
213		179-183	0.53	1% AcOH / 10% MeOH / 89% EtOAc		b	
214		162-164	0.65	1% AcOH / 10% MeOH / 89% EtOAc	509 (M+H)+ [HPLC ES-MS]	b	
215		149-152	0.74	1% AcOH / 10% MeOH / 89% EtOAc	53 (M+H)+ [HPLC ES-MS]	b	
216		121-123	0.50	1% AcOH / 10% MeOH / 89% EtOAc	575 (M+H)+ [HPLC ES-MS]	b	

217		127-129	0.16	50% EtOAc / 50% Hexane	511 (M+H)+ [HPLC ES-MS]	b	
218		110-113	0.26	10% MeOH / 90% CH_2Cl_2	511 (M+H)+ [HPLC ES-MS]	b	
219		123-125	0.29	10% MeOH / 90% CH_2Cl_2	525 (M+H)+ [HPLC ES-MS]	b	
220		144-146	0.19	10% MeOH / 90% CH_2Cl_2	497 (M+H)+ [HPLC ES-MS]	c	

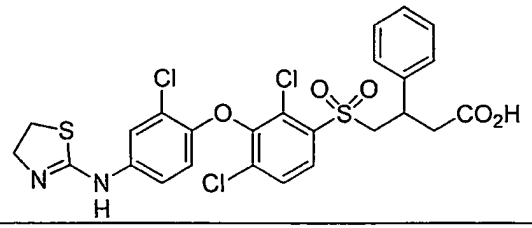
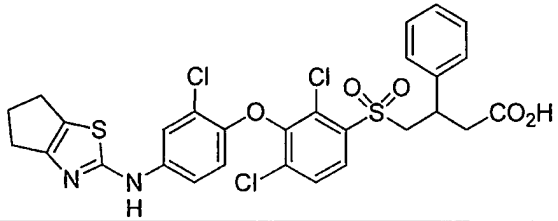
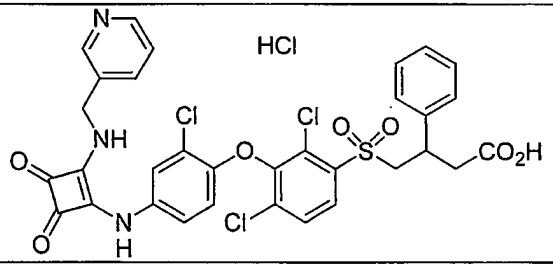
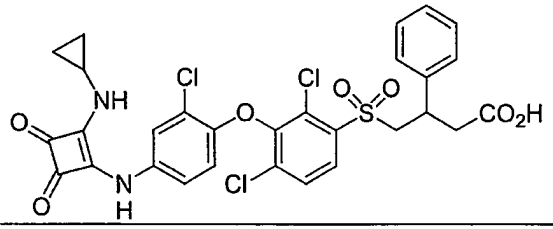
221		112-114	0.58	1% AcOH / 10% MeOH / 89% EtOAc	549 (M+H)+ [HPLC ES-MS]	c	
222		201-203	0.12	10% MeOH / 90% CH_2Cl_2	525 (M+H)+ [HPLC ES-MS]	b	
223		183-184	0.11	10% MeOH / 90% CH_2Cl_2	525 (M+H)+ [HPLC ES-MS]	b	
224		158-160	0.21	10% MeOH / 90% CH_2Cl_2	495 (M+H)+ [HPLC ES-MS]	c	

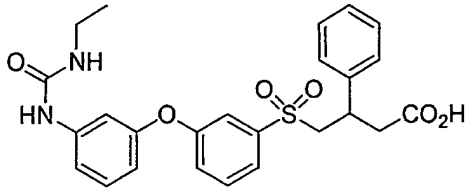
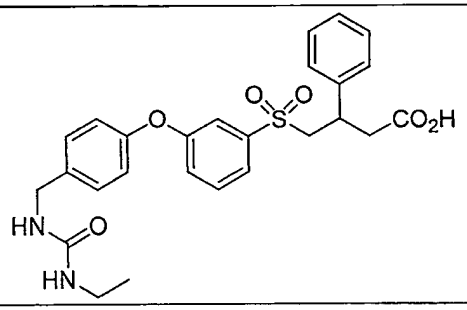
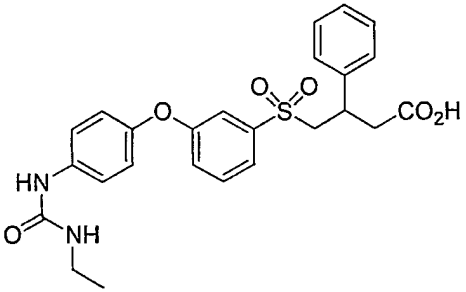
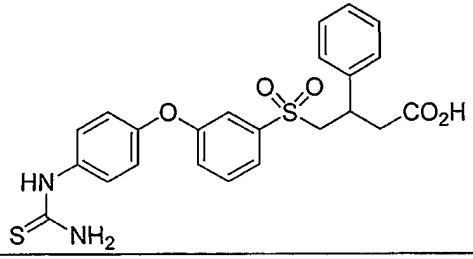
225		123-125	0.27	10% MeOH / 90%		c	
226		120-123	0.23	50% EtOAc / 50% Hexane	523 (M+H)+ [HPLC ES-MS]	c	
227		134-136	0.54	1% AcOH / 10% MeOH / 89% EtOAc		b	c
228		152-154	0.68	1% AcOH / 10% MeOH / 89% EtOAc		b	

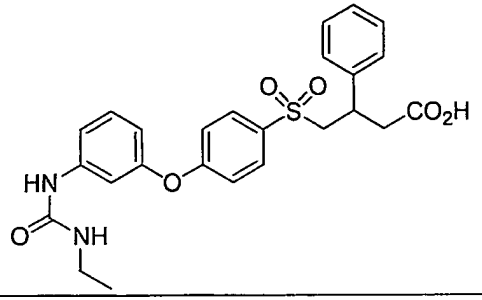
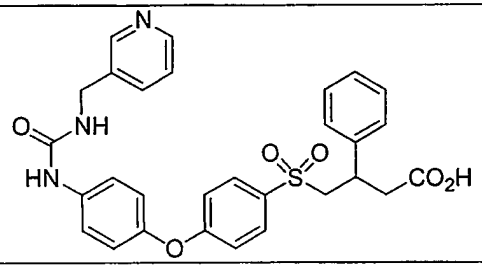
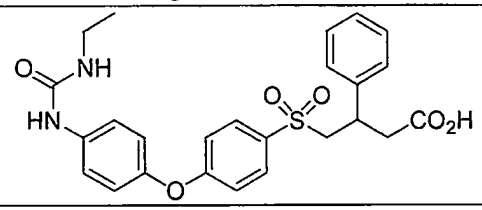
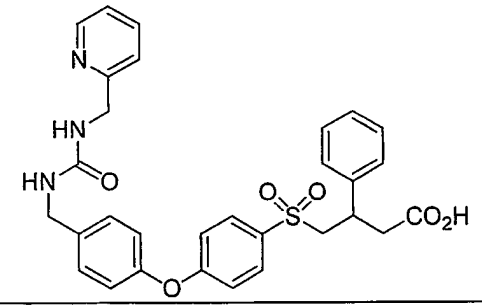
229		114-116	0.61	1% AcOH / 10% MeOH / 89% EtOAc		b	c
230		178-180 (dec)	0.25	10% MeOH / 90% EtOAc		b	
231		188-190	0.58	1% AcOH / 5% MeOH / 94% EtOAc		b	c
232		118-121	0.64	1% AcOH / 10% MeOH / 89% EtOAc		b	

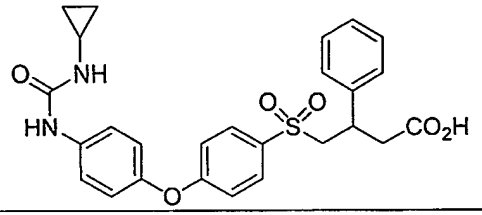
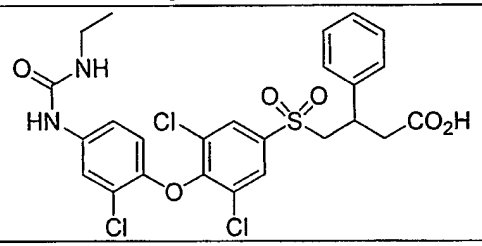
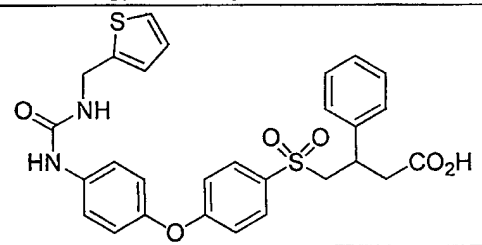
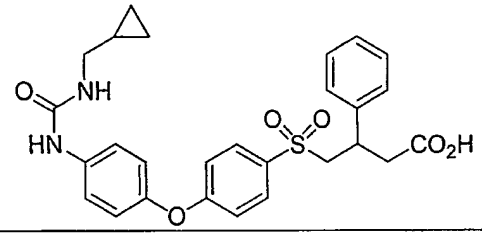
233		98-100	0.58	10% MeOH / 90% EtOAc		b	
234			0.64	1% AcOH / 10% MeOH / 89% EtOAc		b	
235		108-110	0.61	1% AcOH / 10% MeOH / 89% EtOAc		b	
236		203-205	0.63	1% AcOH / 10% MeOH / 89% EtOAc		c	

237		212-214	0.61	1% AcOH / 10% MeOH / 89% EtOAc	c	
238		106-108	0.64	1% AcOH / 10% MeOH / 89% EtOAc	c	
239		192-194 (dec)	0.66	10% MeOH / 90% EtOAc	c	

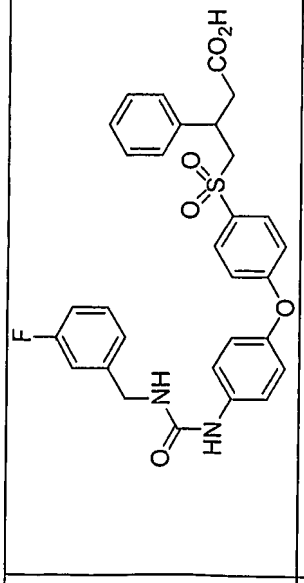
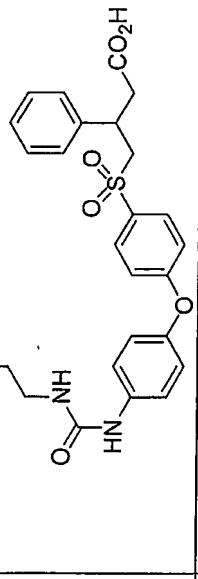
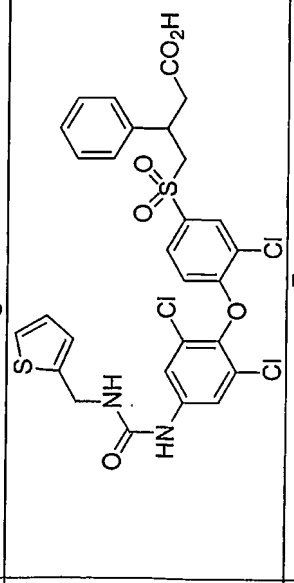
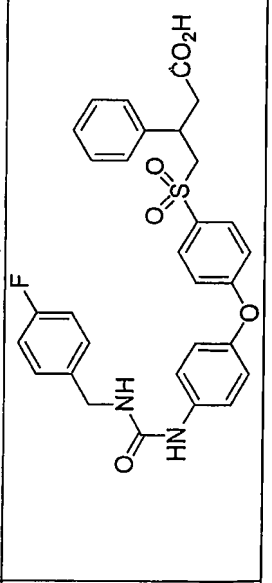
240						a	
241						b	
242				0.01	20% MeOH / 80% CH2CL2		b	
243				0.80	1% AcOH / 10% MeOH / 89% EtOAc		b	

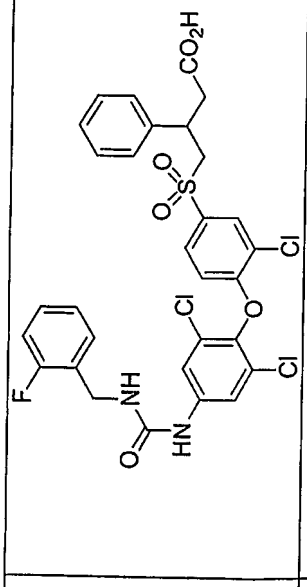
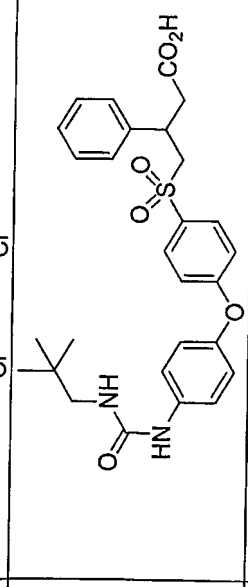
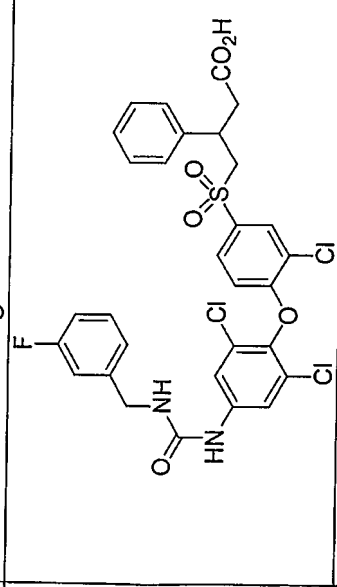
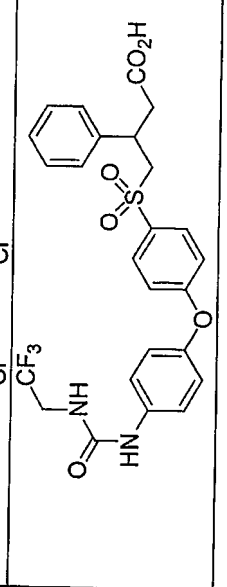
244		90-92	0.28	10% MeOH / 90% EtOAc		b	
245			0.53	1% AcOH / 10% MeOH / 89% EtOAc	497 (M+H)+ [HPLC ES-MS]	c	
246		90-92	0.52	1% AcOH / 5% MeOH / 94% EtOAc		a	
247		133-135	0.46	10% MeOH / 90% EtOAc		b	

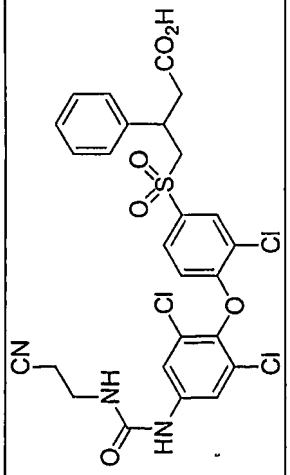
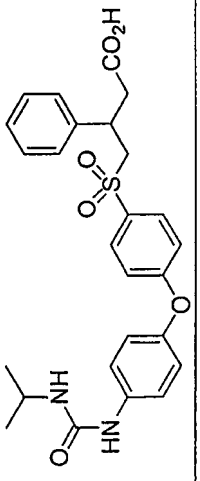
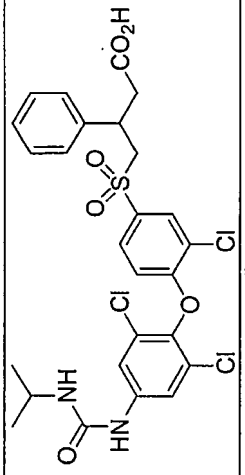
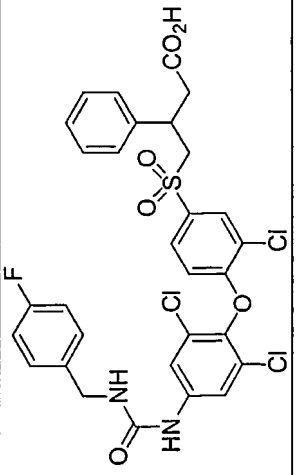
248			0.49	1% AcOH / 5% MeOH / 94% EtOAc		b	
249		149-151	0.20	20% MeOH / 80% CH2CL2	547 (M+H)+ [HPLC ES-MS]	a	c
250		243-245 (dec)	0.55	1% AcOH / 5% MeOH / 94% EtOAc		a	
251		113-115	0.23	1% AcOH / 5% MeOH / 94% EtOAc		a	

252		197-199	0.55	1% AcOH / 5% MeOH / 94% EtOAc		a	
253					585 (M+H)+ [HPLC ES-MS]	a	
254						b	
255						b	

256				611 (M+H)+ [HPLC ES-MS]	b	
257					b	
258				639 (M+H)+ [HPLC ES-MS]	b	
259					b	

260					b	
261					b	
262				653 (M+H)+ [HPLC ES-MS]	b	
263					b	

264				665 (M+H)+ [HPLC ES-MS]	b	
265					c	
266				665 (M+H)+ [HPLC ES-MS]	c	
267					c	

268				610 (M+H)+ [HPLC ES-MS]		c
269						c
270				599 (M+H)+ [HPLC ES-MS]		c
271				665 (M+H)+ [HPLC ES-MS]		c

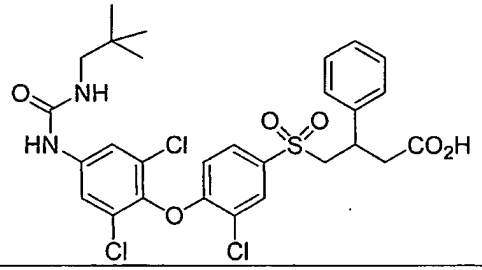
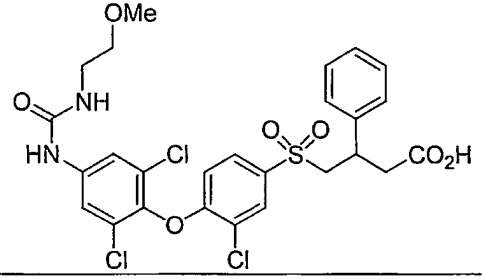
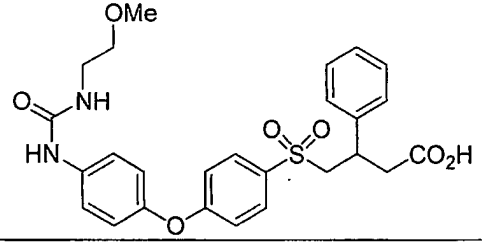
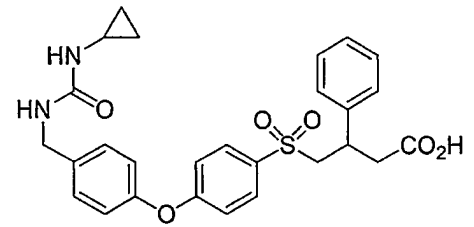
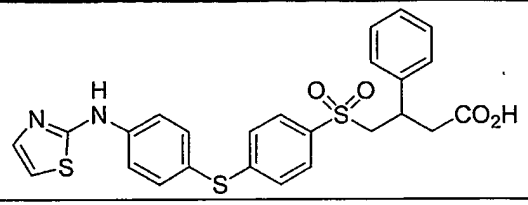
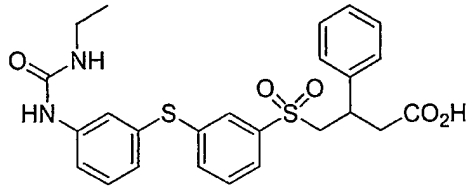
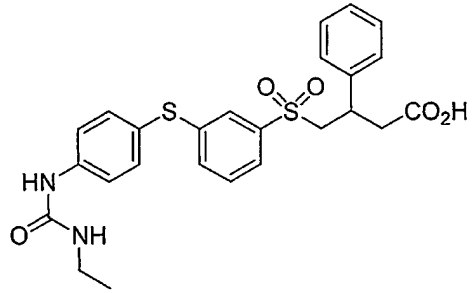
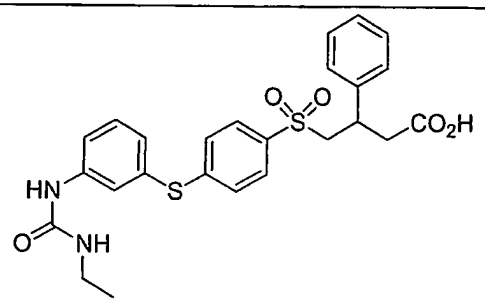
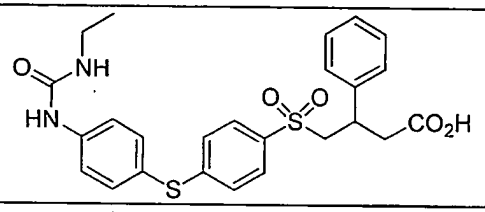
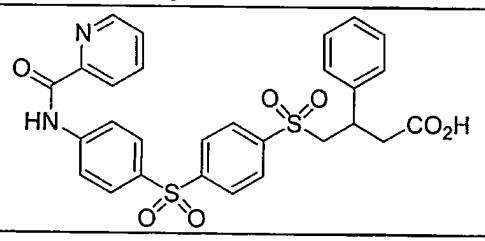
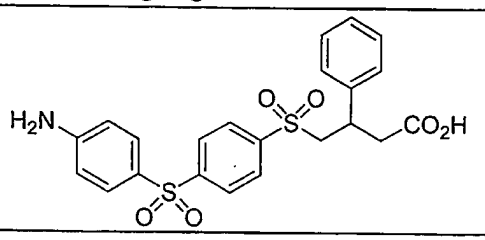
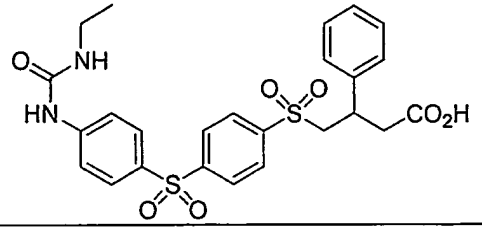
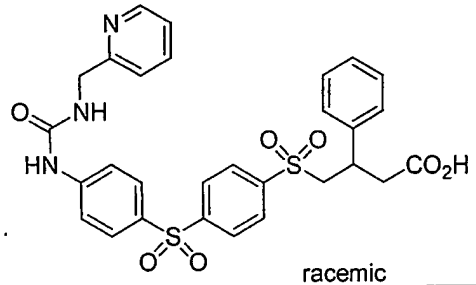
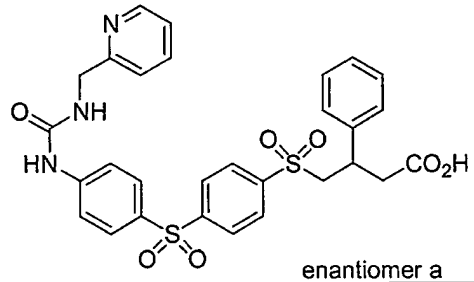
272					627 (M+H)+ [HPLC ES-MS]	c	
273					615 (M+H)+ [HPLC ES-MS]	c	
274						c	
275		101-104	0.53	1% AcOH / 10% MeOH / 89% EtOAc	509 (M+H)+ [HPLC ES-MS]	b	

Table 7.

Ex. #	Butyric Acid	mp (°C)	TLC R_f	Solvent System	Mass Spec.	$\alpha_v\beta_3$ IC_{50}	$\alpha_v\beta_5$ IC_{50}
276					511 (M+H)+ [HPLC ES-MS]	c	
277			0.21	10% MeOH / 90% EtOAc	499 (M+H)+ [HPLC ES-MS]	a	
278			0.26	10% MeOH / 90% EtOAc	499 (M+H)+ [HPLC ES-MS]	a	

279			0.31	10% MeOH / 90% EtOAc	499 (M+H)+ [HPLC ES-MS]	b	
280			0.27	10% MeOH / 90% EtOAc	499 (M+H)+ [HPLC ES-MS]	a	
281			0.62	1% AcOH / 10% MeOH / 89% EtOAc	565 (M+H)+ [HPLC ES-MS]	c	
282			0.35	1% AcOH / 10% MeOH / 89% EtOAc	460 (M+H)+ [HPLC ES-MS]	c	

283			0.19	0.05% AcOH / 95.5% EtOAc	545 (M+H)+ [HPLC ES-MS]	c	
284		196 (dec)	0.60	1% AcOH / 99% EtOAc	531 (M+H)+ [HPLC ES-MS]	a	
285			0.54	1% AcOH / 99% EtOAc	531 (M+H)+ [HPLC ES-MS]	a	
286			0.61	1% AcOH / 99% EtOAc	531 (M+H)+ [HPLC ES-MS]	b	

287		168 (dec)	0.61	1% AcOH / 99% EtOAc	531 (M+H)+ [HPLC ES-MS]	a	
288	 racemic	245-246	0.25	1% AcOH / 10% MeOH / 89% EtOAc	594 (M+H)+ [HPLC ES-MS]	a	c
289	 enantiomer a		0.22	30% MeOH / 70% EtOAc		a	b

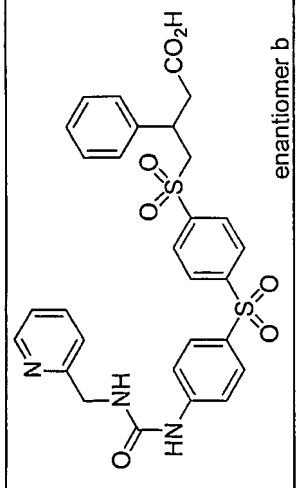
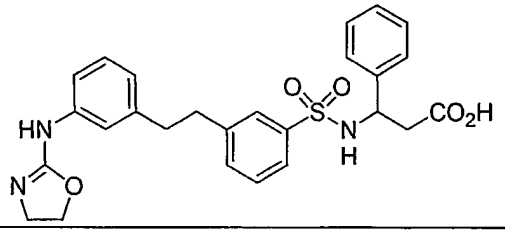
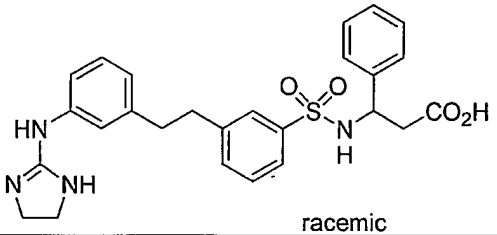
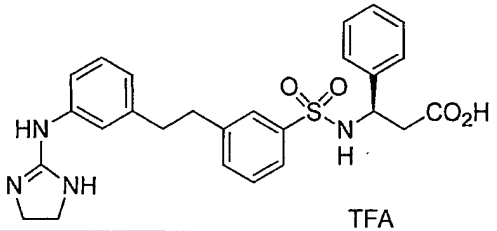
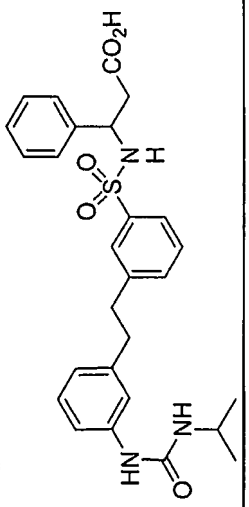
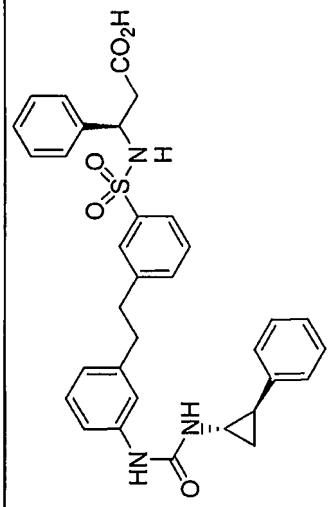
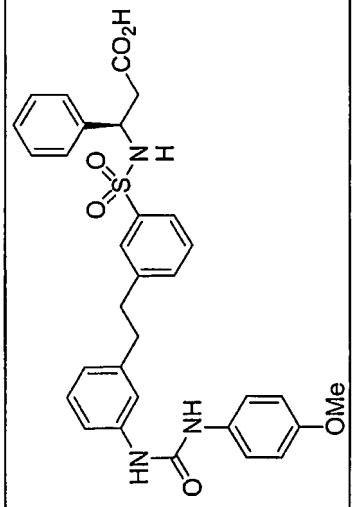
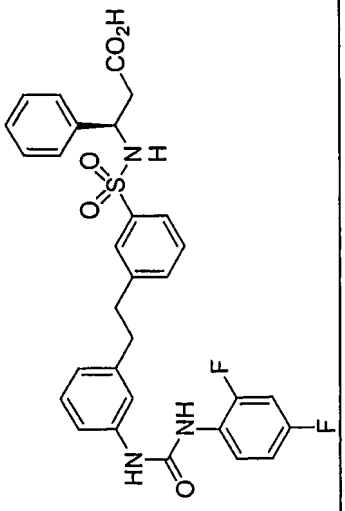
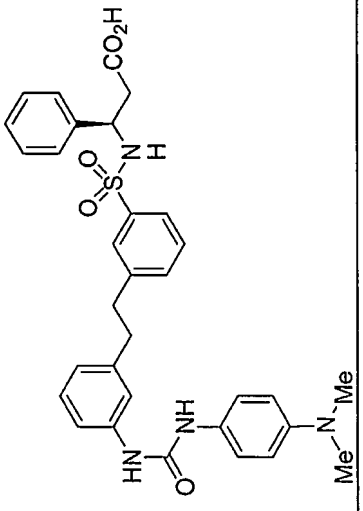
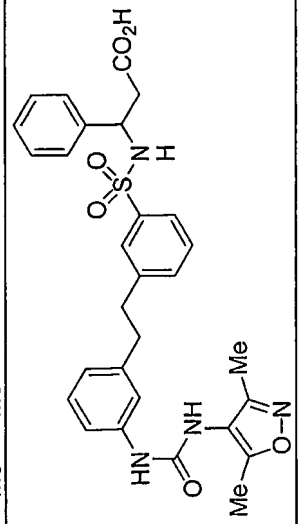
290	 enantiomer b	118	0.22	30% MeOH / 70% EtOAc	b	c

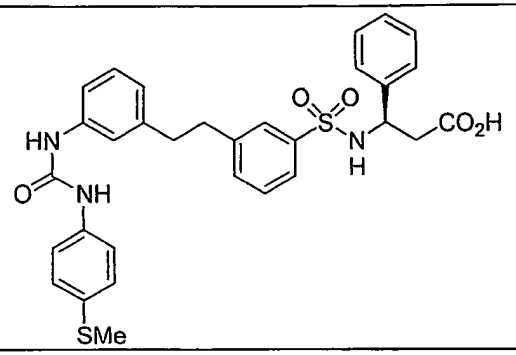
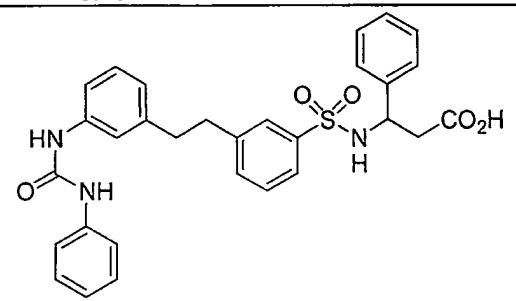
Table 8.

Ex. #	Propionic Acid	mp (°C)	TLC R_f	Solvent System	Mass Spec.	$\alpha v\beta_3$ IC_{50}	$\alpha v\beta_5$ IC_{50}
291					494 (M+H)+ [HPLC ES-MS]	a	
292	 racemic		0.55	20% H2O / 80% CH3CN	493 (M+H)+ [HPLC ES-MS]	a	
293	 TFA		0.55	20% H2O / 80% CH3CN	493 (M+H)+ [HPLC ES-MS]	a	

294			0.55	20% H2O / 80% CH3CN	493 (M+H)+ [HPLC ES-MS]	a	
295	TFA		0.74	20% H2O / 80% CH3CN	493 (M+H)+ [HPLC ES-MS]	a.	b
296						c	
297						a	

298						b
299						b
300						b

301					b
302					c
303					c

304						c	
305			0.60	5% H20 / 5% MeOH / 90% CH3CN	544 (M+H)+ [HPLC ES-MS]	a	

a The compound displayed an IC_{50} of less than or equal to 10 nM in the indicated assay.
b The compound displayed an IC_{50} of greater than 10 nM and less than or equal to 100 nM in the indicated assay.
c The compound displayed an IC_{50} of greater than 100 nM and less than or equal to 1 μM in the indicated assay.

Table 9. Names of Exemplified Compounds

Entry Number	Compound Name
1	4-({4-[({3-[(ethylamino)carbonylamino]phenyl}methyl)amino]phenyl}sulfonyl)-3-phenylbutanoic acid
2	3-phenyl-4-[(4-{[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
3	3-phenyl-4-[(3-{[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
4	3-phenyl-4-[(3-{[4-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
5	3-phenyl-4-[(4-{[4-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
6	4-[(3,5-dichloro-4-{[3-(1,3-thiazolin-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
7	3-phenyl-4-[(4-{[3-(1,3-thiazolin-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
8	3-(3,5-difluorophenyl)-4-[(4-{[3-(1,3-thiazolin-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
9	3-(3-pyridyl)-4-[(4-{[3-(1,3-thiazolin-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
10	4-[(4-{[4-fluoro-3-(1,3-thiazol-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
11	3-(3-pyridyl)-4-[(4-{[3-(1,3-thiazolin-2-ylamino)-5-(trifluoromethyl)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
12	3-phenyl-4-[(4-{[3-(1,3-thiazol-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
13	3-(3-pyridyl)-4-[(4-{[3-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
14	3-phenyl-4-[(4-{[3-(1,3-thiazol-2-ylamino)-5-(trifluoromethyl)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
15	4-[(4-{[2-fluoro-5-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
16	3-phenyl-4-[(4-{[3-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)-5-(trifluoromethyl)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
17	3-(3,5-dichlorophenyl)-4-[(4-{[3-(1,3-thiazol-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
18	4-{[4-({3-[(5-methyl(1,3-thiazolin-2-yl))amino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
19	4-{[4-({3-[(5-methyl(1,3-thiazolin-2-yl))amino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
20	3-phenyl-4-[(4-{[4-(1,3-thiazolin-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
21	4-{[4-({4-[(4,4-dimethyl(1,3-thiazolin-2-yl))amino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
22	3-phenyl-4-[(4-{[3-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenyl]methoxy}phenyl)sulfonyl]butanoic acid
23	4-({4-[(3-{[(1E)-2-aza-2-cyano-1-(methylamino)vinyl]amino}-5-(trifluoromethyl)phenyl)methoxy]phenyl}sulfonyl)-3-(3-pyridyl)butanoic acid
24	4-({4-[(3-{[(1Z)-2-aza-2-cyano-1-(methylamino)vinyl]amino}phenyl)methoxy]phenyl}sulfonyl)-3-(3-pyridyl)butanoic acid
25	4-({4-[(3-{[(1E)-2-aza-2-cyano-1-(methylamino)vinyl]amino}-5-(trifluoromethyl)phenyl)methoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
26	4-({4-[(3-{[(1E)-2-aza-2-cyano-1-(cyclopropylamino)vinyl]amino}phenyl)methoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
27	4-[(4-{[3-({(1E)-2-aza-2-cyano-1-[(3-pyridylmethyl)amino]vinyl}amino)-5-(trifluoromethyl)phenyl]methoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
28	4-({4-[(3-{[(1E)-2-aza-2-cyano-1-(cyclopropylamino)vinyl]amino}-5-(trifluoromethyl)phenyl)methoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
29	4-[(4-{[3-({(1E)-2-aza-2-cyano-1-[(3-pyridylmethyl)amino]vinyl}amino)phenyl]methoxy}phenyl)sulfonyl]-3-(3-pyridyl)butanoic acid
30	4-({4-[(5-{[(1E)-2-aza-2-cyano-1-(methylamino)vinyl]amino}-2-methoxyphenyl)methoxy]phenyl}sulfonyl)-3-phenylbutanoic acid

31	4-({4-[(5-{[(1E)-2-aza-2-cyano-1-(methylamino)vinyl]amino}-2-chlorophenyl)methoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
32	4-({4-[(3-{[(1E)-2-aza-2-cyano-1-(methylamino)vinyl]amino}-4-methylphenyl)methoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
33	4-[(4-{[3-(2-imidazolin-2-ylamino)-5-(trifluoromethyl)phenyl]methoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
34	4-{[4-({3-[(1-methyl(2-imidazolin-2-yl))amino]-5-(trifluoromethyl)phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
35	4-{[4-({3-[(ethylamino)carbonylamino]-4-fluorophenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
36	4-{[4-({3-[(ethylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}-3-(3-pyridyl)butanoic acid
37	4-({4-[(4-fluoro-3-{[(3-pyridylmethyl)amino]carbonylamino}phenyl)methoxy]phenyl}sulfonyl)-3-(3-pyridyl)butanoic acid
38	4-{[4-({2-fluoro-5-[(methylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
39	3-(3-pyridyl)-4-({4-[(3-{[(3-pyridylmethyl)amino]carbonylamino}phenyl)methoxy]phenyl}sulfonyl)butanoic acid
40	4-{[4-({3-[(cyclopropylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
41	3-phenyl-4-({4-[(3-{[(2,2,2-trifluoroethyl)amino]carbonylamino}phenyl)methoxy]phenyl}sulfonyl)butanoic acid
42	4-{[4-({3-[(methylamino)carbonylamino]-5-(trifluoromethyl)phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
43	4-{[4-({4-chloro-3-[(methylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
44	4-{[4-({2-methoxy-5-[(methylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
45	3-phenyl-4-({4-[(3-{[(3-pyridylmethyl)amino]carbonylamino}-5-(trifluoromethyl)phenyl)methoxy]phenyl}sulfonyl)butanoic acid
46	3-(4-chloro-3-fluorophenyl)-4-({4-[(3-{[(3-pyridylmethyl)amino]carbonylamino}phenyl)methoxy]phenyl}sulfonyl)butanoic acid
47	4-{[4-({3-[(cyclopropylamino)carbonylamino]-5-(trifluoromethyl)phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
48	3-phenyl-4-({4-[(3-{[(3-pyridylmethyl)amino]carbonylamino}phenyl)methoxy]phenyl}sulfonyl)butanoic acid
49	4-{[4-({4-methyl-3-[(methylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
50	4-({4-[(3-{[(3-pyridylmethyl)amino]carbonylamino}phenyl)methoxy]phenyl}sulfonyl)-3-[4-(trifluoromethyl)phenyl]butanoic acid
51	4-{[4-({2-chloro-5-[(methylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
52	3-phenyl-4-({4-[(3-{[benzylamino]carbonylamino}phenyl)methoxy]phenyl}sulfonyl)butanoic acid
53	3-phenyl-4-{[4-({3-[(phenylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}butanoic acid
54	4-{[4-({5-[(cyclopropylamino)carbonylamino]-2-methoxyphenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
55	4-{[4-({4-chloro-3-[(cyclopropylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
56	3-(3,5-dichlorophenyl)-4-{[4-({3-[(ethylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}butanoic acid
57	4-({4-[(3-{[(2-morpholin-4-ylethyl)amino]carbonylamino}phenyl)methoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
58	4-{[4-({3-[(cyclopropylamino)carbonylamino]-4-methylphenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
59	3-(3,5-dichlorophenyl)-4-({4-[(3-{[(methylethyl)amino]carbonylamino}phenyl)methoxy]phenyl}sulfonyl)butanoic acid
60	4-{[4-({4-[(ethylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
61	4-{[4-({3-[(ethylamino)carbonylamino]phenyl}methoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
62	3-phenyl-4-[(4-{[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenoxy]methyl}phenyl)sulfonyl]butanoic acid
63	3-phenyl-4-[(4-{[3-(1,3-thiazolin-2-ylamino)phenoxy]methyl}phenyl)sulfonyl]butanoic acid
64	3-phenyl-4-[(4-{2-[3-(2-pyridylcarbonylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
65	4-{[4-(2-{3-[2-(methylamino)acetylamino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid

66	3-phenyl-4-[(4-{2-[3-(propanoylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
67	3-phenyl-4-[(4-{2-[3-(1,3-thiazol-4-ylcarbonylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid, 2,2,2-trifluoroacetic acid
68	4-{[4-(2-{3-[(imino-2-thienylmethyl)amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
69	3-phenyl-4-[(4-{2-[3-(1-pyrrolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
70	4-{[4-(2-{3-[(iminophenylmethyl)amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
71	4-{[4-(2-{3-[(5-oxo(1-pyrrolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
72	4-({4-[2-(3-aminophenyl)ethyl]phenyl}sulfonyl)-3-phenylbutanoic acid
73	(3R)-4-{[4-(2-{3-[(2-aminoethyl)amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
74	4-({4-[2-(2-aminobenzothiazol-5-yl)ethyl]phenyl}sulfonyl)-3-phenylbutanoic acid
75	4-[(4-{2-[3-(1,3-oxazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
76	4-({4-[2-(6-amino(3-pyridyl))ethyl]phenyl}sulfonyl)-3-phenylbutanoic acid
77	4-[(4-{2-[6-(2,5-dimethylpyrrolyl)(3-pyridyl)]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
78	(3R)-3-phenyl-4-[(4-{2-[3-(2-pyridylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
79	3-phenyl-4-{[4-(2-{3-[(2-pyridylmethyl)amino]phenyl}ethyl)phenyl]sulfonyl}butanoic acid
80	3-(4-fluorophenyl)-4-[(4-{2-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
81	3-(4-fluorophenyl)-4-[(4-{2-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
82	3-(4-fluorophenyl)-4-[(4-{2-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
83	4-[(4-{2-[4-fluoro-3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
84	4-[(3-chloro-4-{2-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-(4-fluorophenyl)butanoic acid
85	(3R)-4-[(4-{2-[2-methoxy-5-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
86	3-phenyl-4-[(4-{2-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
87	(3R)-3-phenyl-4-{[4-(2-{3-[(4H,5H,6H-1,3-thiazin-2-ylamino)methyl]phenyl}ethyl)phenyl]sulfonyl}butanoic acid
88	3-phenyl-4-[(3-{2-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
89	3-phenyl-4-[(3-{2-[4-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
90	3-phenyl-4-[(4-{2-[4-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
91	3-phenyl-4-[(4-{2-[3-(1,3-thiazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
92	(3R)-3-phenyl-4-{[4-(2-{3-[(1,3-thiazolin-2-ylamino)methyl]phenyl}ethyl)phenyl]sulfonyl}butanoic acid
93	3-phenyl-4-[(4-{2-[3-(1,3-thiazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
94	4-{[4-(2-{3-[(5-methyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
95	4-{[4-(2-{3-[(4-methyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
96	(3R)-4-{[4-(2-{3-[(4-methyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
97	3-phenyl-4-[(4-{2-[4-(1,3-thiazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
98	3-(4-fluorophenyl)-4-[(4-{2-[3-(1,3-thiazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
99	4-[(3-chloro-4-{2-[3-(1,3-thiazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-(4-fluorophenyl)butanoic acid
100	4-[(4-{2-[4-fluoro-3-(1,3-thiazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid

101	3-(4-fluorophenyl)-4-[(4-{2-[3-(1,3-thiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
102	3-(4-fluorophenyl)-4-[(4-{2-[3-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
103	(3R)-4-[(4-{2-[2-methoxy-5-(1,3-thiazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
104	(3R)-4-{[4-(2-{5-[(4,4-dimethyl(1,3-thiazolin-2-yl))amino]-2-methoxyphenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
105	(3R)-4-[(4-{2-[2-methoxy-5-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
106	(3R)-4-[(4-{2-[2-methoxy-5-(1,3-thiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
107	3-phenyl-4-[(4-{2-[3-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
108	4-{[4-(2-{3-[(4,5-dimethyl(1,3-thiazol-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
109	3-phenyl-4-{[4-(2-{3-[(4-phenyl(1,3-thiazol-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}butanoic acid
110	4-{[4-(2-{3-[(4-methyl(1,3-thiazol-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
111	4-[(4-{2-[3-(benzothiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
112	4-{[4-(2-{3-[(4,4-dimethyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
113	(3R)-4-{[4-(2-{3-[(4,4-dimethyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
114	4-{[3-(2-{4-[(4,4-dimethyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
115	4-{[3-(2-{3-[(4,4-dimethyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
116	4-{[4-(2-{3-[(4,5-dimethyl(1,3-thiazol-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-(3-pyridyl)butanoic acid
117	3-phenyl-4-{[4-(2-{3-[(5-phenyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}butanoic acid
118	4-{[4-(2-{3-[(4-oxo(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
119	4-{[4-(2-{3-[(1-aza-3-thiaspiro[4.4]non-1-en-2-yl)amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
120	4-{[4-(2-{3-[(4-methyl-5-phenyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
121	4-{[4-(2-{3-[(5-methyl-4-oxo(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
122	(3R)-4-{[4-(2-{3-[(5-methyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
123	(3R)-4-{[4-(2-{3-[(5,5-dimethyl(1,3-thiazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
124	3-phenyl-4-[(4-{2-[3-(1,3-thiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
125	(3R)-3-phenyl-4-[(4-{2-[3-(1,3-thiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
126	(3S)-3-phenyl-4-[(4-{2-[3-(1,3-thiazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
127	4-{[4-(2-{3-[(4,5-dimethyl(1,3-thiazol-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
128	4-({4-[2-(3-{[(1E)-2-aza-2-cyano-1-(methylamino)vinyl]amino}phenyl)ethyl]phenyl}sulfonyl)-3-(4-fluorophenyl)butanoic acid
129	3-(4-fluorophenyl)-4-[(4-{2-[3-(3,4,5,6-tetrahydropyrimidin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
130	4-{[4-(2-{3-[(5,5-dimethyl(2-imidazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-(4-fluorophenyl)butanoic acid
131	3-(4-fluorophenyl)-4-[(4-{2-[3-(2-imidazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]butanoic acid
132	4-{[4-(2-{3-[(5,5-dimethyl(3,4,5,6-tetrahydropyrimidin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-(4-fluorophenyl)butanoic acid
133	(3R)-4-{[4-(2-{3-[(5-hydroxy(3,4,5,6-tetrahydropyrimidin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
134	(3R)-4-[(4-{2-[3-(2-iminoimidazolidinyl)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
135	(3R)-4-[(4-{2-[3-(benzimidazol-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid, 2,2,2-trifluoroacetic acid

136	4-{[4-(2-{3-[(4-oxo(2-imidazolin-2-yl))amino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid, 2,2,2-trifluoroacetic acid
137	4-[(4-{2-[3-(2-imidazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
138	4-[(3-{2-[3-(2-imidazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]-3-phenylbutanoic acid
139	4-({4-[2-(3-{[4-(cyclopropylamino)-2,3-dioxocyclobut-1(4)-enyl]amino}phenyl)ethyl]phenyl}sulfonyl)-3-phenylbutanoic acid
140	4-{[4-(2-{4-fluoro-3-[(methylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
141	4-{[4-(2-{3-[(ethylamino)carbonylamino]-4-fluorophenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
142	4-{[4-(2-{3-[(ethylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
143	(3R)-4-{[4-(2-{3-[(ethylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}-3-phenylbutanoic acid
144	3-phenyl-4-({4-[2-(3-{[(2-pyridylmethyl)amino]carbonylamino}phenyl)ethyl]phenyl}sulfonyl)butanoic acid
145	4-{[4-(2-{3-[(cyclopropylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}-3-(2-fluorophenyl)butanoic acid
146	3-(2-chlorophenyl)-4-{[4-(2-{3-[(cyclopropylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}butanoic acid
147	3-(2-fluorophenyl)-4-({4-[2-(3-{[(2-pyridylmethyl)amino]carbonylamino}phenyl)ethyl]phenyl}sulfonyl)butanoic acid
148	4-{[4-(2-{3-[(ethylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}-3-[3-(trifluoromethyl)phenyl]butanoic acid
149	4-{[4-(2-{3-[(cyclopropylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}-3-(4-phenoxyphenyl)butanoic acid
150	3-(2-chlorophenyl)-4-{[4-(2-{4-[(cyclopropylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}butanoic acid
151	3-[3,5-bis(trifluoromethyl)phenyl]-4-{[4-(2-{3-[(cyclopropylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}butanoic acid
152	3-(4-phenoxyphenyl)-4-({4-[2-(3-{[(2-pyridylmethyl)amino]carbonylamino}phenyl)ethyl]phenyl}sulfonyl)butanoic acid
153	3-(4-cyanophenyl)-4-({4-[2-(4-{[(2-pyridylmethyl)amino]carbonylamino}phenyl)ethyl]phenyl}sulfonyl)butanoic acid
154	3-(4-cyanophenyl)-4-({4-[2-(3-{[(2-pyridylmethyl)amino]carbonylamino}phenyl)ethyl]phenyl}sulfonyl)butanoic acid
155	3-(4-cyanophenyl)-4-{[4-(2-{3-[(cyclopropylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}butanoic acid
156	3-(4-cyanophenyl)-4-{[4-(2-{4-[(cyclopropylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}butanoic acid
157	3-phenyl-4-[(4-{2-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]ethynyl}phenyl)sulfonyl]butanoic acid
158	3-phenyl-4-[(4-{2-[3-(1,3-thiazolin-2-ylamino)phenyl]ethynyl}phenyl)sulfonyl]butanoic acid
159	3-phenyl-4-[(4-{2-[3-(1,3-thiazol-2-ylamino)phenyl]ethynyl}phenyl)sulfonyl]butanoic acid
160	4-[(4-{(1E)-2-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]vinyl}phenyl)sulfonyl]-3-phenylbutanoic acid, 2,2,2-trifluoroacetic acid
161	4-[(4-{(1E)-2-[3-(1,3-thiazolin-2-ylamino)phenyl]vinyl}phenyl)sulfonyl]-3-phenylbutanoic acid, 2,2,2-trifluoroacetic acid
162	4-({4-[(4-aminophenyl)carbonyl]phenyl}sulfonyl)-3-phenylbutanoic acid
163	4-[(4-{[4-[(5-hydroxy(3,4,5,6-tetrahydropyrimidin-2-yl))amino]phenyl}carbonyl)phenyl]sulfonyl}-3-phenylbutanoic acid
164	3-phenyl-4-[(4-{[4-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]carbonyl}phenyl)sulfonyl]butanoic acid
165	4-[(4-{(1E)-2-aza-2-methoxy-1-[4-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]vinyl}phenyl)sulfonyl]-3-phenylbutanoic acid
166	4-[(4-{(1Z)-2-aza-2-methoxy-1-[4-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]vinyl}phenyl)sulfonyl]-3-phenylbutanoic acid
167	3-phenyl-4-[(4-{[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]carbonyl}phenyl)sulfonyl]butanoic acid
168	4-{[4-({4-[(5-methyl(1,3-thiazolin-2-yl))amino]phenyl}carbonyl)phenyl]sulfonyl}-3-phenylbutanoic acid
169	4-{[4-({4-[(4-methyl(1,3-thiazolin-2-yl))amino]phenyl}carbonyl)phenyl]sulfonyl}-3-phenylbutanoic acid
170	3-phenyl-4-[(4-{[4-(1,3-thiazolin-2-ylamino)phenyl]carbonyl}phenyl)sulfonyl]butanoic acid

171	3-phenyl-4-[(4-{[4-(1,3-thiazol-2-ylamino)phenyl]carbonyl}phenyl)sulfonyl]butanoic acid
172	4-{[4-({4-[(4,4-dimethyl(1,3-thiazolin-2-yl))amino]phenyl}carbonyl)phenyl]sulfonyl}-3-phenylbutanoic acid
173	3-phenyl-4-[(4-{[3-(1,3-thiazolin-2-ylamino)phenyl]carbonyl}phenyl)sulfonyl]butanoic acid
174	3-phenyl-4-[(4-{[3-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenyl]carbonyl}phenyl)sulfonyl]butanoic acid
175	4-[(4-{difluoro[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]methyl}phenyl)sulfonyl]-3-phenylbutanoic acid
176	4-[(4-{difluoro[3-(1,3-thiazolin-2-ylamino)phenyl]methyl}phenyl)sulfonyl]-3-phenylbutanoic acid
177	4-[(4-{[4-(ethylamino)phenyl]methyl}phenyl)sulfonyl]-3-phenylbutanoic acid
178	3-phenyl-4-{[4-({4-[(4H,5H,6H-1,3-thiazin-2-ylamino)methyl]phenyl}methyl)phenyl]sulfonyl}butanoic acid
179	3-phenyl-4-[(4-{[4-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]methyl}phenyl)sulfonyl]butanoic acid
180	4-{[4-({4-[(4-methyl(1,3-thiazolin-2-yl))amino]phenyl}methyl)phenyl]sulfonyl}-3-phenylbutanoic acid
181	3-phenyl-4-[(4-{[4-(1,3-thiazolin-2-ylamino)phenyl]methyl}phenyl)sulfonyl]butanoic acid
182	3-phenyl-4-{[4-({4-[(1,3-thiazolin-2-ylamino)methyl]phenyl}methyl)phenyl]sulfonyl}butanoic acid
183	4-{[4-({4-[(5-methyl(1,3-thiazolin-2-yl))amino]phenyl}methyl)phenyl]sulfonyl}-3-phenylbutanoic acid
184	4-[(4-{hydroxy[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenyl]methyl}phenyl)sulfonyl]-3-phenylbutanoic acid
185	4-[(4-{hydroxy[3-(1,3-thiazolin-2-ylamino)phenyl]methyl}phenyl)sulfonyl]-3-phenylbutanoic acid
186	3-phenyl-4-({3-[4-(2-pyridylcarbonylamino)phenoxy]phenyl}sulfonyl)butanoic acid
187	3-phenyl-4-({4-[4-(2-pyridylcarbonylamino)phenoxy]phenyl}sulfonyl)butanoic acid
188	4-{[3-(4-aminophenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
189	4-{[4-(4-aminophenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
190	4-{[3-(2-aminobenzothiazol-6-yloxy)phenyl]sulfonyl}-3-phenylbutanoic acid
191	4-{[4-(2-aminobenzothiazol-5-yloxy)phenyl]sulfonyl}-3-phenylbutanoic acid
192	3-phenyl-4-[(3-{4-[(2-pyridylamino)methyl]phenoxy}phenyl)sulfonyl]butanoic acid
193	4-[(4-{4-[(4-methyl(2-pyridyl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
194	3-phenyl-4-({4-[4-(2-pyridylamino)phenoxy]phenyl}sulfonyl)butanoic acid
195	3-phenyl-4-({3-[4-(2-pyridylamino)phenoxy]phenyl}sulfonyl)butanoic acid
196	4-[(4-{4-[(4-methyl(2-quinolyl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
197	3-phenyl-4-({3-[4-(4H,5H,6H-1,3-thiazin-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
198	3-phenyl-4-({4-[3-(4H,5H,6H-1,3-thiazin-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
199	4-[(4-{4-[(5-methyl(1,3-thiazolin-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
200	4-[(4-{4-[(4-methyl(1,3-thiazolin-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
201	3-phenyl-4-({4-[4-(4H,5H,6H-1,3-thiazin-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
202	4-[(4-{4-[(4,4-dimethyl(1,3-thiazolin-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
203	3-phenyl-4-({4-[4-(1,3-thiazolin-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
204	4-[(3-{4-[(4,4-dimethyl(1,3-thiazolin-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
205	3-(3-pyridyl)-4-({4-[4-(1,3-thiazolin-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid

206	4-[(3-{4-[(4-methyl(1,3-thiazolin-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
207	3-phenyl-4-[(4-{4-[(1,3-thiazolin-2-ylamino)methyl]phenoxy}phenyl)sulfonyl]butanoic acid
208	3-phenyl-4-[(4-{4-[(4H,5H,6H-1,3-thiazin-2-ylamino)methyl]phenoxy}phenyl)sulfonyl]butanoic acid
209	3-phenyl-4-({3-[4-(1,3-thiazolin-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
210	3-phenyl-4-[(3-{4-[(1,3-thiazolin-2-ylamino)methyl]phenoxy}phenyl)sulfonyl]butanoic acid
211	4-[(3-{4-[(5-methyl(1,3-thiazolin-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
212	3-phenyl-4-[(3-{4-[(4H,5H,6H-1,3-thiazin-2-ylamino)methyl]phenoxy}phenyl)sulfonyl]butanoic acid
213	3-(3-pyridyl)-4-({4-[4-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
214	3-phenyl-4-[(4-{4-[(1,3-thiazol-2-ylamino)methyl]phenoxy}phenyl)sulfonyl]butanoic acid
215	3-phenyl-4-({4-[4-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
216	4-({4-[3-bromo-4-(1,3-thiazolin-2-ylamino)phenoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
217	4-[(4-{3-[(5-methyl(1,3-thiazolin-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
218	4-[(4-{3-[(4-methyl(1,3-thiazolin-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
219	4-[(4-{3-[(4,4-dimethyl(1,3-thiazolin-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
220	3-phenyl-4-({4-[3-(1,3-thiazolin-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
221	3-phenyl-4-[(3-{4-[(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)methyl]phenoxy}phenyl)sulfonyl]butanoic acid
222	4-{[4-(4-{[(5-methyl(1,3-thiazolin-2-yl))amino]methyl}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
223	4-{[4-(4-{[(4-methyl(1,3-thiazolin-2-yl))amino]methyl}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
224	3-phenyl-4-({4-[3-(1,3-thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
225	3-phenyl-4-({4-[3-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
226	4-[(4-{4-[(4,5-dimethyl(1,3-thiazol-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
227	3-phenyl-4-({3-[4-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
228	4-{[4-(4-{[4-(4-fluorophenyl)(1,3-thiazol-2-yl)]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
229	4-[(3-{4-[(4,5-dimethyl(1,3-thiazol-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
230	4-[(4-{4-[(4-methyl(1,3-thiazol-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
231	3-phenyl-4-({4-[4-(1,3-thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
232	4-[(3-{4-[(4-methyl(1,3-thiazol-2-yl))amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
233	3-phenyl-4-({3-[4-(1,3-thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
234	3-phenyl-4-[(3-{4-[(4-phenyl(1,3-thiazol-2-yl))amino]phenoxy}phenyl)sulfonyl]butanoic acid
235	3-phenyl-4-({3-[4-(4,5,6,7-tetrahydrobenzothiazol-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
236	4-({4-[4-(benzothiazol-2-ylamino)phenoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
237	4-{[3-(4-{[4-(4-fluorophenyl)(1,3-thiazol-2-yl)]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
238	4-{[3-(4-{[4-(tert-butyl)(1,3-thiazol-2-yl)]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
239	3-phenyl-4-({3-[3-(1,3-thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)butanoic acid
240	4-({3,5-dichloro-4-[2-chloro-4-(1,3-thiazolin-2-ylamino)phenoxy]phenyl}sulfonyl)-3-phenylbutanoic acid

241	4-({3,5-dichloro-4-[2-chloro-4-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-ylamino)phenoxy]phenyl}sulfonyl)-3-cyclohexa-2,4-dienylbutanoic acid
242	4-({4-[4-({2,3-dioxo-4-[(3-pyridylmethyl)amino]cyclobut-1(4)-enyl}amino)phenoxy]phenyl}sulfonyl)-3-phenylbutanoic acid, chloride
243	4-{[4-(4-{[4-(cyclopropylamino)-2,3-dioxocyclobut-1(4)-enyl]amino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
244	4-[(3-{3-[(ethylamino)carbonylamino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
245	4-{[3-(4-{[(ethylamino)carbonylamino]methyl}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
246	4-[(3-{4-[(ethylamino)carbonylamino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
247	4-[(3-{4-[(aminothioxomethyl)amino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
248	4-[(4-{3-[(ethylamino)carbonylamino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
249	3-(3-pyridyl)-4-{[4-(4-{[(3-pyridylmethyl)amino]carbonylamino}phenoxy)phenyl]sulfonyl}butanoic acid
250	4-[(4-{4-[(ethylamino)carbonylamino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
251	3-phenyl-4-{[4-(4-{[(2-pyridylmethyl)amino]carbonylamino}phenoxy)phenyl]sulfonyl}butanoic acid
252	4-[(4-{4-[(cyclopropylamino)carbonylamino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
253	4-[(3,5-dichloro-4-{2-chloro-4-[(ethylamino)carbonylamino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
254	3-phenyl-4-{[4-(4-{[(2-thienylmethyl)amino]carbonylamino}phenoxy)phenyl]sulfonyl}butanoic acid
255	4-{[4-(4-{[(cyclopropylmethyl)amino]carbonylamino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
256	4-{[4-(2,6-dichloro-4-{[(cyclopropylmethyl)amino]carbonylamino}phenoxy)-3-chlorophenyl]sulfonyl}-3-phenylbutanoic acid
257	4-[(3,5-dichloro-4-{2-chloro-4-[(cyclopropylamino)carbonylamino]phenoxy}phenyl)sulfonyl]-3-phenylbutanoic acid
258	4-{[4-(2,6-dichloro-4-{[(2,2,2-trifluoroethyl)amino]carbonylamino}phenoxy)-3-chlorophenyl]sulfonyl}-3-phenylbutanoic acid
259	4-({4-[4-({[(2-fluorophenyl)methyl]amino}carbonylamino)phenoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
260	4-({4-[4-({[(3-fluorophenyl)methyl]amino}carbonylamino)phenoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
261	4-{[4-(4-{[(2-cyanoethyl)amino]carbonylamino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
262	4-{[4-(2,6-dichloro-4-{[(2-thienylmethyl)amino]carbonylamino}phenoxy)-3-chlorophenyl]sulfonyl}-3-phenylbutanoic acid
263	4-({4-[4-({[(4-fluorophenyl)methyl]amino}carbonylamino)phenoxy]phenyl}sulfonyl)-3-phenylbutanoic acid
264	4-({4-[2,6-dichloro-4-({[(2-fluorophenyl)methyl]amino}carbonylamino)phenoxy]-3-chlorophenyl}sulfonyl)-3-phenylbutanoic acid
265	4-{[4-(4-{[(2,2-dimethylpropyl)amino]carbonylamino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
266	4-({4-[2,6-dichloro-4-({[(3-fluorophenyl)methyl]amino}carbonylamino)phenoxy]-3-chlorophenyl}sulfonyl)-3-phenylbutanoic acid
267	3-phenyl-4-{[4-(4-{[(2,2,2-trifluoroethyl)amino]carbonylamino}phenoxy)phenyl]sulfonyl}butanoic acid
268	4-{[4-(2,6-dichloro-4-{[(2-cyanoethyl)amino]carbonylamino}phenoxy)-3-chlorophenyl]sulfonyl}-3-phenylbutanoic acid
269	4-{[4-(4-{[(methylethyl)amino]carbonylamino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
270	4-{[4-(2,6-dichloro-4-{[(methylethyl)amino]carbonylamino}phenoxy)-3-chlorophenyl]sulfonyl}-3-phenylbutanoic acid
271	4-({4-[2,6-dichloro-4-({[(4-fluorophenyl)methyl]amino}carbonylamino)phenoxy]-3-chlorophenyl}sulfonyl)-3-phenylbutanoic acid
272	4-{[4-(4-{[(2,2-dimethylpropyl)amino]carbonylamino}-2,6-dichlorophenoxy)-3-chlorophenyl]sulfonyl}-3-phenylbutanoic acid
273	4-{[4-(2,6-dichloro-4-{[(2-methoxyethyl)amino]carbonylamino}phenoxy)-3-chlorophenyl]sulfonyl}-3-phenylbutanoic acid
274	4-{[4-(4-{[(2-methoxyethyl)amino]carbonylamino}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid
275	4-{[4-(4-{[(cyclopropylamino)carbonylamino]methyl}phenoxy)phenyl]sulfonyl}-3-phenylbutanoic acid

276	3-phenyl-4-({4-[4-(1,3-thiazol-2-ylamino)phenylthio]phenyl}sulfonyl)butanoic acid
277	4-[(3-{3-[(ethylamino)carbonylamino]phenylthio}phenyl)sulfonyl]-3-phenylbutanoic acid
278	4-[(3-{4-[(ethylamino)carbonylamino]phenylthio}phenyl)sulfonyl]-3-phenylbutanoic acid
279	4-[(4-{3-[(ethylamino)carbonylamino]phenylthio}phenyl)sulfonyl]-3-phenylbutanoic acid
280	4-[(4-{4-[(ethylamino)carbonylamino]phenylthio}phenyl)sulfonyl]-3-phenylbutanoic acid
281	3-phenyl-4-[(4-{[4-(2-pyridylcarbonylamino)phenyl]sulfonyl}phenyl)sulfonyl]butanoic acid
282	4-({4-[(4-aminophenyl)sulfonyl]phenyl}sulfonyl)-3-phenylbutanoic acid
283	3-phenyl-4-[(3-{[3-(1,3-thiazolin-2-ylamino)phenyl]sulfonyl}phenyl)sulfonyl]butanoic acid
284	4-{[3-({3-[(ethylamino)carbonylamino]phenyl}sulfonyl)phenyl]sulfonyl}-3-phenylbutanoic acid
285	4-{[3-({4-[(ethylamino)carbonylamino]phenyl}sulfonyl)phenyl]sulfonyl}-3-phenylbutanoic acid
286	4-{[4-({3-[(ethylamino)carbonylamino]phenyl}sulfonyl)phenyl]sulfonyl}-3-phenylbutanoic acid
287	4-{[4-({4-[(ethylamino)carbonylamino]phenyl}sulfonyl)phenyl]sulfonyl}-3-phenylbutanoic acid
288	3-phenyl-4-({4-[(4-{[(2-pyridylmethyl)amino]carbonylamino}phenyl)sulfonyl]phenyl}sulfonyl)butanoic acid
289	3-phenyl-4-({4-[(4-{[(2-pyridylmethyl)amino]carbonylamino}phenyl)sulfonyl]phenyl}sulfonyl)butanoic acid
290	3-phenyl-4-({4-[(4-{[(2-pyridylmethyl)amino]carbonylamino}phenyl)sulfonyl]phenyl}sulfonyl)butanoic acid
291	3-{[(3-{2-[3-(1,3-oxazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]amino}-3-phenylpropanoic acid
292	3-{[(3-{2-[3-(2-imidazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]amino}-3-phenylpropanoic acid
293	(3R)-3-{[(3-{2-[3-(2-imidazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]amino}-3-phenylpropanoic acid, 2,2,2-trifluoroacetic acid
294	(3S)-3-{[(3-{2-[3-(2-imidazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]amino}-3-phenylpropanoic acid, 2,2,2-trifluoroacetic acid
295	3-{[(4-{2-[3-(2-imidazolin-2-ylamino)phenyl]ethyl}phenyl)sulfonyl]amino}-3-phenylpropanoic acid
296	(3R)-3-({[3-(2-{3-[(ethylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}amino)-3-phenylpropanoic acid
297	(3R)-3-({[3-(2-{3-[(cyclopropylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}amino)-3-phenylpropanoic acid
298	3-[({3-[2-(3-{[(methylethyl)amino]carbonylamino}phenyl)ethyl]phenyl}sulfonyl)amino]-3-phenylpropanoic acid
299	(3R)-3-[({3-[2-(3-{[N-((1S,2R)-2-phenylcyclopropyl)carbamoyl]amino}phenyl)ethyl]phenyl}sulfonyl)amino]-3-phenylpropanoic acid
300	(3R)-3-[({3-[2-(3-{[(4-methoxyphenyl)amino]carbonylamino}phenyl)ethyl]phenyl}sulfonyl)amino]-3-phenylpropanoic acid
301	(3R)-3-[({3-[2-(3-{[(2,4-difluorophenyl)amino]carbonylamino}phenyl)ethyl]phenyl}sulfonyl)amino]-3-phenylpropanoic acid
302	(3R)-3-{[(3-{2-[3-({[4-(dimethylamino)phenyl]amino}carbonylamino)phenyl]ethyl}phenyl)sulfonyl]amino}-3-phenylpropanoic acid
303	3-[({3-[2-(3-{[(3,5-dimethylisoxazol-4-yl)amino]carbonylamino}phenyl)ethyl]phenyl}sulfonyl)amino]-3-phenylpropanoic acid
304	(3R)-3-[({3-[2-(3-{[(4-methylthiophenyl)amino]carbonylamino}phenyl)ethyl]phenyl}sulfonyl)amino]-3-phenylpropanoic acid
305	3-phenyl-3-({[3-(2-{3-[(phenylamino)carbonylamino]phenyl}ethyl)phenyl]sulfonyl}amino)propanoic acid

Description of Treatment of Diseases or Conditions Associated with $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin

Integrins are heterodimeric transmembrane proteins found on the surface of cells, which play an important part in the adhesion of the cells to an extracellular matrix. They recognize extracellular glycoproteins such as fibronectin or vitronectin on the extracellular matrix by means of the RGD sequence occurring in these proteins (RGD is the single letter code for the amino acid sequence arginine-glycine-aspartate).

The vitronectin integrin is a member of the integrin family and refers to three different integrins, $\alpha_v\beta_1$; $\alpha_v\beta_3$ and $\alpha_v\beta_5$. Each of these integrins play an important part in biological processes such as cell migration and cell-matrix adhesion and in diseases/conditions where these processes are crucial steps. These diseases/conditions include angiogenesis, arteriosclerosis, cancer, ophthalmia and osteoporosis and restenosis (Schoop et al., WO 00/41469; Albers et al. WO 00/35864; Sugrue et al., U.S. Patent 5,900,414 which is hereby incorporated by reference); diabetic retinopathy, and conditions related to inhibition of bone resorption (which includes osteoporosis, hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease and immobilization-induced osteopenia) (Duggan et al., WO 99/30713, WO 99/30709, WO 98/31359 and WO 98/08840; Chen et al., U.S. Patent 5,852,210 which are hereby incorporated by reference); macular degeneration (Duggan et al., *ibid.*); and inflammation and viral disease (Askew et al., WO 99/31061; Chen et al., U.S. Patent 5,852,210 which are hereby incorporated by reference).

The $\alpha_v\beta_3$ integrin binds to a wide range of ligands including fibrin, fibrinogen, laminin, thrombospondin, vitronectin, von Willebrand's factor, osteospontin and bone sialoprotein I (Brooks et al., U.S. Patent 5,766,591 which is hereby incorporated by reference) which explains the association of the wide variety of diseases and conditions mentioned above with the $\alpha_v\beta_3$ integrin.

The $\alpha_v\beta_3$ integrin is responsible for the interaction between osteoclasts, i.e. cells resorbing mineralized tissue, and the bone structure. The first step in the degradation of bone tissue is the adhesion of osteoclasts to the bone. This cell-matrix interaction takes place via the $\alpha_v\beta_3$ integrin, which is why the corresponding integrin plays an important part in this process (S.B. Rodan et al., *J. Endocrinology*, vol. 154: S47-S56, (1997) which is hereby incorporated

by reference). Osteolytic diseases such as osteoporosis are induced by an inequilibrium between bone formation and bone destruction, i.e. the resorption of bone material caused by accumulation of osteoclasts predominates.

The degradation of bone tissue can be suppressed by blockage of the $\alpha_v\beta_3$ integrins of the osteoclasts, since these are then unable to accumulate on the bone in order to absorb its substance (Hoffman et al., WO 98/18461; Fisher et al., *Endocrinology*, vol. 132: 1411, (1993) which are hereby incorporated by reference).

It is well known in the art that angiogenesis plays a significant role in the establishment or exacerbation of a number of disorders including blindness (macular degeneration, diabetic retinopathy, corneal transplant. myopic degeneration), inflammation (arthritis, psoriasis, inflammatory bowel disease) and solid tumor cancer (lung, breast, prostate, colon, bladder, pancreas, melanoma, renal, glioblastoma, neuroblastoma, etc.) (cf. Varner, "The role of vascular cell integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ in angiogenesis", from Regulation of Angiogenesis, ed. Goldberg and Rosen, publ. Birkhäuser Verlag, pages 361-390, (1997) which is hereby incorporated by reference)

The $\alpha_v\beta_3$ integrin occurs in large amounts on growing endothelial cells (as well as being expressed on other cell types such as smooth muscle, osteoclasts and tumor cells) and makes possible their adhesion to an extracellular matrix. As such, the $\alpha_v\beta_3$ integrin plays an important part in angiogenesis, which is a crucial prerequisite for tumor growth and metastasis formation in carcinoses.

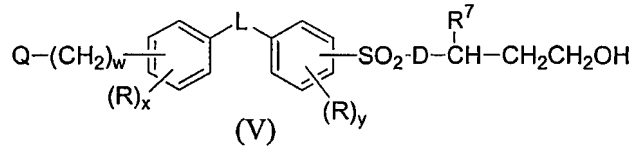
It has also been shown that the blockage of the $\alpha_v\beta_3$ integrin is an important starting point for the treatment of disorders of this type. If the adhesion of growing endothelial cells to an extracellular matrix is suppressed by blocking the $\alpha_v\beta_3$ integrin, for example, by a cyclic peptide or a monoclonal antibody, the endothelial cells die. Therefore, angiogenesis does not occur, which leads to a cessation or regression of the growth tumor (Brooks et al., *Cell*, vol. 79: 1157-1164, (1994) which is hereby incorporated by reference) and the invasive properties of tumor cells and their capability for metastasis formation are markedly decreased if their $\alpha_v\beta_3$ integrin is blocked by an antibody (Brooks et al., *J. Clin. Invest.*, vol. 96: 1815, (1995) which is hereby incorporated by reference).

Likewise, it has been reported by Varner that administering antagonists for $\alpha_v\beta_5$ integrin has been efficacious in blocking VGEF, TGF-α and PMA-induced angiogenesis (Varner, *ibid.* and Friedlander et al., *Science*, vol. 270: 1500-1502, (1995) each of which is hereby incorporated by reference).

By means of the blockage of the $\alpha_v\beta_3$ integrin on cells of the smooth aorta vascular musculature with the aid of integrin integrin antagonists, the migration of these cells into the neointima and thus angioplasty leading to arteriosclerosis and restenosis can be suppressed (Brown et al., *Cardiovascular Res.*, vol. 28: 1815, (1994) which is hereby incorporated by reference). Restenosis is also thought to be prevented by antagonists of $\alpha_v\beta_3$ integrin or $\alpha_v\beta_5$ integrin as the antagonists act to prevent the binding of osteopontin, a ligand for $\alpha_v\beta_3$ integrin or $\alpha_v\beta_5$ integrin which is implicated in the calcification of atherosclerotic plaques (Varner, *ibid.*)

Therefore, the state of the art supports that the administering of compounds which are antagonists of the $\alpha_v\beta_3$ integrin or $\alpha_v\beta_5$ integrin will be efficacious in the treatment of diseases and conditions related to the $\alpha_v\beta_3$ integrin or $\alpha_v\beta_5$ integrin.

For the purpose of the method of treatment of diseases and conditions related to the $\alpha_v\beta_3$ integrin or $\alpha_v\beta_5$ integrin, the scope of the compounds used also includes compounds which have the formula (V):



(V)

wherein the variables w, x, y, Q, R, L, D and R^7 are as defined for the compound of formula (I). The difference between the compound of formula (I) and (V) is the presence of a -CH_2OH in formula (V) in place of -CO_2R^{11} in formula (I). The compounds of formula (V) are prodrugs of compounds of formula (I) capable of undergoing biotransformation *in vivo* to afford the active carboxylic acid.

Other embodiments of the invention will be apparent to the skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended

that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

Biological Protocols

$\alpha_v\beta_3$ Binding Assay: $\alpha_v\beta_3$ from human A375 cells was purified analogously to a procedure which was described by Wong et al. (*Molecular Pharmacology*, vol. 50, pages 529-537, (1996) - which is hereby incorporated by reference). In each case, 10 µL of $\alpha_v\beta_3$ (5 ng) in TBS pH 7.6, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 1% n-octyl-glucopyranoside (Sigma); 10 µL of test compound in TBS pH 7.6, 0.1% DMSO and 45 µL of TBS pH 7.6, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 1 mM $MnCl_2$ were incubated at room temperature for 1 h. In each case, 25 µL of WGA SPA beads (Amersham, 4 mg/mL) and 10 µL of echistatin (0.1 µCi, Amersham, chloramine-T labelled) were then added. After 16 hours at room temperature, the samples were measured in a scintillation measuring apparatus (Wallac 1450).

All of the compounds in Tables 1 - 8 had an IC_{50} less than or equal to 1 µM. Selected compounds identified in Tables 1 - 8 also had an IC_{50} less than or equal to 10 nM.

Bone Resorption Assay: Resorption of bone by osteoclasts was measured by analysis of resorption pits excavated by osteoclasts on slices of bovine femur. In performing the *in vitro* bone resorption assay, five-day-old rabbits were euthanized, their limbs removed and the cells from the bones were isolated. The cells were counted and plated onto bovine cortical bone chips(4 mm x 4 mm x 400 microns) in 96-well plates containing compounds to be tested and the appropriate controls. After 48 h, the chips were washed (0.1 M cacodylate buffer, 0.25 M NH_4OH, H_2O, acetone), and stained (1% toluidine blue in 1% borax) to highlight the resorption pits. The pits were counted under a light microscope and averages were determined.

Angiogenesis Inhibition Assay: Using a modified version of the mouse Matrigel model of angiogenesis described by Kerr et al. (*Anticancer Res.*, 19: 959-968, (1999) which is hereby incorporated by reference), the selected compounds were tested for angiogenesis inhibiting activity.

Growth inhibition test on tumor cell lines: The human large intestine cell lines SW 480 and HT29 (ATCC No. CCL 228 and HTB38), the human breast cell lines MDA-MB 231, MCF-7 and BT-20 (ATCC No. HTB-, 26, 22 and 23) and the mouse melanoma cell line B16F10 (CRL 6475) were grown to confluence in Roux dishes in RPMI 1640 medium with addition of 10% FCS. They were then trypsinized and taken up in RPMI plus 10% FCS to a cell count of 50,000 cells or, for B16F10, 20,000 cell per mL. 100 µL of cell suspension/well were added to a 96 microwell plate and incubated at 37 °C for 1 day in a CO_2 incubator. A further 100 µL of RPMI medium and 1 µL of DMSO were then added with the test substances. The growth was checked after day 6. For this, 25 µL of MTT solution (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added to each starting well at a starting concentration of 5 mg/mL of H_2O. The plate was incubated at 37 °C for 5 hours in a CO_2 incubator. The medium was then aspirated and 100 µL of isopropanol/well were added. After shaking with 100 µL of H_2O for 30 min., the extinction was measured at 595 nm using a Multiplate Reader (BIO-RAD 3550-UV). Cystostatic action is indicated as an IC_{50} value.

In vivo inhibition of tumor growth:

Material: In all *in vivo* experiments investigating the inhibition of tumor growth, athymic nude mice (NMRI nu/nu strain) were used. The tumor was developed by serial passage in nude mice. The human origin of the tumor was confirmed by isoenzymatic and immunohistochemical methods.

Experimental Setup: The tumor was implanted subcutaneously in both flanks of nu/nu nude mice 6 to 8 weeks old. The treatment was started, depending on the doubling time, as soon as the tumors had reached a diameter of 5 - 7 mm. The mice assigned to the treatment group or the control group (5 mice per group having 8 - 10 assessable tumors) by randomization. The individual tumors of the control group all grew progressively.

The size of the tumors was measured in two dimensions by means of a slide gauge. The tumor volume, which correlated well with the cell count, was then used for all assessments. The volume was calculated according to the formula "length x breadth x breadth/2" ([a x b^2]/ 2. wherein a and b represent two diameters arranged at right angles.

The values of the relative tumor volume (RTV) were calculated for each individual tumor by dividing the tumor size on day X with the tumor size on day 0 (at the time of randomization). The average values of the RTV were then used for further assessment.

The inhibition of the increase of the tumor volume (tumor volume of the test group/control group, T/C, in percent) was the final measured value.

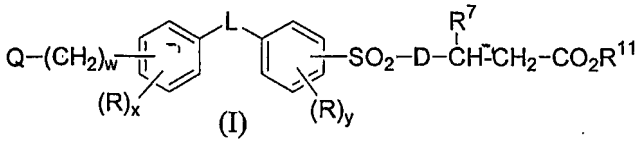
Treatment: The compounds can be administered with a daily or an intermittent therapy schedule through a couple of days by intraperitoneal, intravenous, oral or subcutaneous means.

CSF-induced proliferation of hemapoietic stem cells: Bone marrow cells were flushed out of the femur mice. 10^5 cells were incubated in McCoy 5A medium (0.3% agar) together with recombinant murine GM-CSF (Genzyme, parent cell colony formation) and the substances (10^{-4} to 100 μg/mL) at 37 °C and 7% CO_2. Seven days later, the colonies (<50 cells) and clusters (17-50 cells) were counted.

Other embodiments of the invention will be apparent to the skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the scope and spirit of the invention being indicated by the following claims.

WE CLAIM:

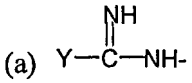
1. A compound of formula (I)



(I)

wherein:

Q is a substituent selected from the group consisting of:

(a) 

wherein

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_3-C_5-alkenyl,

(a5) C_4-C_8-cycloalkenyl,

(a6) C_3-C_5-alkynyl,

(a7) C_6-C_{10}-aryl,

(a8) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(a9) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(a10) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and -NZ^1Z^2; and

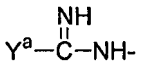
(a2) - (a10) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from

the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or $-NZ^1Z^2$, wherein

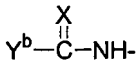
Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

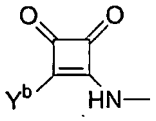
Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

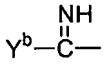
(b) 

wherein Y^a represents $-NH_2$ or -NH-Y;

(c) 

wherein X represents O, S or N(CN) ;

(d) 

(e) 

wherein for (c) - (e)

Y^b represents $-NH_2$, -NH-Y or -Y;

(f) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(f1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one

to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(f2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(f2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(f2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (f1) - (f2) are optionally substituted by R;

(g) Y^c=N-

wherein Y^c is as defined in (f) above;

(h) Y^dY^e-N-

wherein Y^d and Y^e are independently selected from the group consisting of hydrogen, C_1-C_5-alkyl, and C_1-C_5-aminoalkyl;

and

(i) when w = 0, Q forms a four to eight membered heterocyclic ring fused to the aryl group to which it is attached to form a bicyclic ring, wherein said heterocyclic ring contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and

at least one carbon atom and said heterocyclic ring is optionally substituted with C_1-C_5-alkyl or $-NZ^3Z^4$ wherein Z^3 and Z^4 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1,

(g) $C(=O)OR^1$,

(h) $S(=O)_2OR^1$,

(i) NR^1R^2,

(j) $C(=O)NR^1R^2$, and

(k) $S(=O)_2NR^1R^2$;

wherein for (f)-(k):

R^1 and R^2 independently represent a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

or

wherein for (i)-(k):

R^1 and R^2 together with the nitrogen to which it is attached represents a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) O,

(b) C(=O),

(c) CR^3R^4,

(d) $N(R^5)$,

(e) $S(=O)_z$,

(f) $C(=O)N(R^5)$,

(g) $N(R^5)C(=O)$,

(h) $S(=O)_2N(R^5)$

(i) $N(R^5)S(=O)_2$,

(j) CR^3R^4-CR^3R^4,

(k) CH_2O,

(l) OCH_2,

(m) $CH_2N(R^5)$,

(n) $N(R^5)CH_2$,

(o) CH=CH,

(p) -C≡C- ; and

(q) $C(=NR^3)$

R^3 and R^4 independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) C_1-C_3-alkyl, and

(4) C_1-C_3-alkoxy;

wherein:

when one or two R^3 groups are C_1-C_3-alkyl in L, said one or two R^3 groups may constitute spiro rings or nonspiro rings wherein:

(a) one group R^3 is joined by a bond or by a heteroatom selected from the group consisting of oxygen, nitrogen and sulfur, to the carbon chain to which said group R^3

is attached, and taken together with the carbon chain atom(s) to which said group R^3 is attached, constitutes a ring of three to six members,

wherein for CR^3R^4, when R^3 is C_1-alkyl, the R^3 group is joined by a heteratom as defined above, or

(b) two groups R^3 are joined by a bond or by a heteroatom selected from the group consisting of oxygen, nitrogen and sulfur and taken together with the carbon chain atom(s) to which said two groups R^3 are attached, constitute a ring of 3-6 members; or

R^5 represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

D represents a substituent selected from the group consisting of:

(a) $(CH_2)_v$ and

(b) $N(R^6)$

wherein R^6 represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

and wherein:

L is not $C(=O)N(R^5)$, $N(R^5)C(=O)$, $S(=O)_2N(R^5)$ or $N(R^5)S(=O)_2$- when D is -NH-;

R^7 represents a substituent selected from the group consisting of:

(a) C_2-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_2-C_5-alkynyl,

where (a)-(f) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (g)-(j) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_2OH$,

(5) $S(=O)_nR^{10}$,

(6) $S(=O)_2NR^8R^9$,

(7) NR^8R^9,

(8) OR^8,

(9) $C(=O)R^{10}$,

(10) $C(=O)OR^8$; or

(11) $C(=O)NR^8R^9$;

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (g) – (j) are substituted by NR^8R^9, $S(=O)_2NR^8R^9$ or $C(=O)NR^8R^9$,

R^8 and R^9 together with the nitrogen to which it is attached represents a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl;

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_3-C_5-alkynyl,

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (a)-(j) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl,

(c) C_3-C_6-cycloalkyl,

(d) C_3-C_6-alkenyl,

(e) C_5-C_6-cycloalkenyl, and

(f) C_3-C_6-alkynyl

wherein (b)-(f) are optionally substituted by:

(1) halogen,

(2) OR^{12}, or

(3) $NR^{12}R^{13}$;

wherein

R^{12} and R^{13} independently represent hydrogen or C_1-C_3-alkyl;

or

R^{12} and R^{13} together with the nitrogen to which it is attached represents a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

u is an integer from 0 - 2;

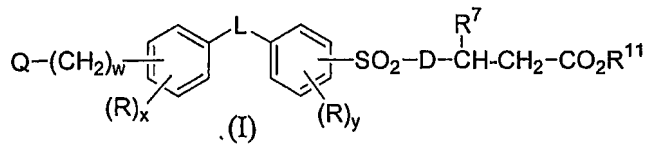
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

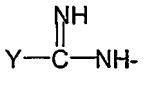
2. The compound of claim 1 having the formula



(I)

wherein

Q is a substituent selected from the group consisting of:

(a) 

wherein

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_4-C_8-cycloalkenyl,

(a5) C_6-C_{10}-aryl,

(a6) C_6-C_{10}-aryl-C_1-C_3-alkyl, and

(a7) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and -NZ^1Z^2; and

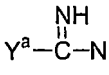
(a2) - (a7) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or -NZ^1Z^2,

wherein

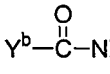
Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

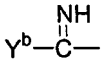
or

Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

(b) 

wherein Y^a represents $-NH_2$ or -NH-Y;

(c)  ;

(d)  ;

wherein for (c) - (d)

Y^b represents $-NH_2$, -NH-Y or -Y;

(e) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(e1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(e2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered

saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(e2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(e2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (e1) - (e2) are optionally substituted by R;

(f) Y^c=N-

wherein Y^c is as defined in (e) above;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1, and

(g) NR^1R^2,

wherein for (f) and (g),

R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, and

(3) C_3-C_8-cycloalkyl;

or

wherein for (g),

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) CR^3R^4-CR^3R^4,

(b) CH_2O,

(c) OCH_2,

(d) CH=CH, and

(e) -C≡C- ;

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_3-alkyl, and

(3) C_1-C_3-alkoxy;

D represents NH;

R^7 represents a substituent selected from the group consisting of:

(a) C_3-C_8-cycloalkyl,

(b) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(c) C_3-C_5-alkenyl,

(d) C_4-C_8-cycloalkenyl,

(e) C_2-C_5-alkynyl,

where (a)-(e) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(f) C_6-C_{10}-aryl,

(g) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(h) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(i) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (f)-(i) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_nR^{10}$,

(5) NR^8R^9,

(6) OR^8, or

(7) $C(=O)R^{10}$,

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (f) – (i) are substituted by NR^8R^9,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl; and

wherein (a)-(c) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl,

(c) C_3-C_6-cycloalkyl,

(d) C_3-C_6-alkenyl,

(e) C_5-C_6-cycloalkenyl, and

(f) C_3-C_6-alkynyl

wherein (b)-(f) are optionally substituted by:

(1) halogen, or

(2) OR^{12},

wherein

R^{12} represents hydrogen or C_1-C_3-alkyl;

u is an integer from 0 - 2;

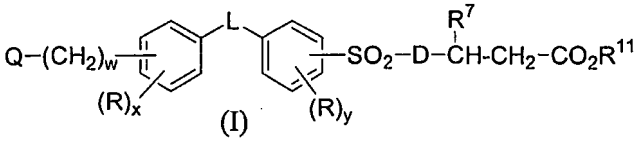
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

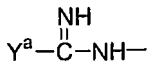
3. The compound of claim 2 having the formula



(I)

wherein

Q is a substituent selected from the group consisting of:

(a) 

wherein

Y^a represents $-NH_2$ or -NH-Y; and

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_4-C_8-cycloalkenyl,

(a5) C_6-C_{10}-aryl,

(a6) C_6-C_{10}-aryl-C_1-C_3-alkyl, and

(a7) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and $-NZ^1Z^2$; and

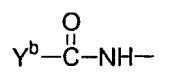
(a2) - (a7) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or $-NZ^1Z^2$,

wherein

Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

(b) 

wherein Y^b represents $-NH_2$, -NH-Y or -Y;

(c) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(c1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(c2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(c2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(c2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (c1) - (c2) are optionally substituted by R;

(d) Y^c=N-

wherein Y^c is as defined in (c) above;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1, and

(g) NR^1R^2,

wherein for (f) and (g),

R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, and

(3) C_3-C_8-cycloalkyl;

or

wherein for (g),

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) CR^3R^4-CR^3R^4,

(b) CH_2O, and

(c) OCH_2,

R^3 and R^4 each independently represents H;

D represents NH;

R^7 represents a substituent selected from the group consisting of:

(a) C_3-C_8-cycloalkyl,

(b) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(c) C_3-C_5-alkenyl,

(d) C_4-C_8-cycloalkenyl,

(e) C_2-C_5-alkynyl,

where (a)-(e) are optionally substituted by

(1) OR^8, or

(2) halogen;

(f) C_6-C_{10}-aryl,

(g) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(h) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(i) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (f)-(i) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_nR^{10}$,

(5) NR^8R^9,

(6) OR^8, or

(7) $C(=O)R^{10}$,

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (f) – (i) are substituted by NR^8R^9,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl; and

wherein (a)-(c) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl, and

(c) C_3-C_6-cycloalkyl,

wherein (a)-(c) are optionally substituted by:

(1) halogen, or

(2) OR^{12},

wherein

R^{12} represents hydrogen or C_1-C_3-alkyl;

u is an integer from 0 - 2;

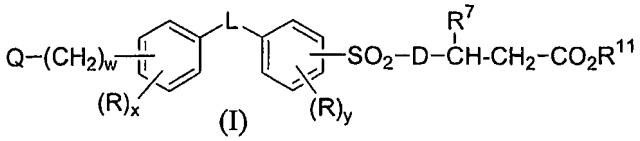
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

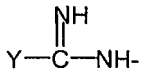
4. The compound of claim 1 having the formula



(I)

wherein

Q is a substituent selected from the group consisting of:

(a) 

wherein

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_3-C_5-alkenyl,

(a5) C_4-C_8-cycloalkenyl,

(a6) C_3-C_5-alkynyl,

(a7) C_6-C_{10}-aryl,

(a8) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(a9) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(a10) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

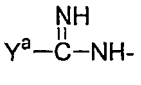
(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and -NZ^1Z^2; and

(a2) - (a10) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or -NZ^1Z^2, wherein

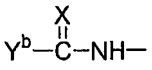
Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

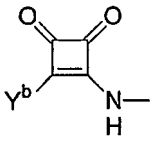
Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

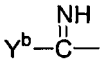
(b) 

wherein Y^a represents $-NH_2$ or -NH-Y;

(c) 

wherein X represents O or N(CN) ;

(d)  ;

(e) 

wherein for (c) - (e)

Y^b represents $-NH_2$, -NH-Y or -Y;

(f) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(f1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(f2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(f2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(f2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (f1) - (f2) are optionally substituted by R;

(g) Y^c=N-

wherein Y^c is as defined in (f) above;

(h) Y^dY^e-N-

wherein Y^d and Y^e are independently selected from the group consisting of hydrogen, C_1-C_5-alkyl, and C_1-C_5-aminoalkyl;

and

(i) when w = 0, Q forms a four to eight membered heterocyclic ring fused to the aryl group to which it is attached to form a bicyclic ring, wherein said heterocyclic ring contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and at least one carbon atom and said heterocyclic ring is optionally substituted with C_1-C_5-alkyl or -NZ^3Z^4 wherein Z^3 and Z^4 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1,

(g) $C(=O)OR^1$,

(h) $S(=O)_2OR^1$,

(i) NR^1R^2,

(j) $C(=O)NR^1R^2$, and

(k) $S(=O)_2NR^1R^2$;

wherein for (f)-(k):

R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

or

wherein for (i)-(k):

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) O,

(b) C(=O),

(c) CR^3R^4,

(d) $N(R^5)$,

(e) $S(=O)_z$, and

(f) $C(=NR^3)$

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_3-alkyl, and

(3) C_1-C_3-alkoxy;

wherein:

when an R^3 group is C_1-C_3-alkyl in L, said R^3 group may constitute a spiro or nonspiro ring wherein:

(a) the group R^3 is joined by a bond or by a heteroatom selected from the group consisting of oxygen, nitrogen and sulfur, to the carbon chain to which said group R^3 is attached, and taken together with the carbon chain atom(s) to which said group R^3 is attached, constitutes a ring of three to six members,

wherein for CR^3R^4, when R^3 is C_1-alkyl, the R^3 group is joined by a heteratom as defined above;

R^5 represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

D represents CH_2 ;

R^7 represents a substituent selected from the group consisting of:

(a) C_2-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_2-C_5-alkynyl,

where (a)-(f) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (g)-(j) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_2OH$,

(5) $S(=O)_nR^{10}$,

(6) $S(=O)_2NR^8R^9$,

(7) NR^8R^9,

(8) OR^8,

(9) $C(=O)R^{10}$,

(10) $C(=O)OR^8$; or

(11) $C(=O)NR^8R^9$;

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (g) – (j) are substituted by NR^8R^9, $S(=O)_2NR^8R^9$ or $C(=O)NR^8R^9$,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl;

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_3-C_5-alkynyl,

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (a)-(j) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl,

(c) C_3-C_6-cycloalkyl,

(d) C_3-C_6-alkenyl,

(e) C_5-C_6-cycloalkenyl, and

(f) C_3-C_6-alkynyl

wherein (b)-(f) are optionally substituted by:

(1) halogen,

(2) OR^{12}, or

(3) $NR^{12}R^{13}$;

wherein

R^{12} and R^{13} each independently represents hydrogen or C_1-C_3-alkyl;

or

R^{12} and R^{13} together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional

heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

u is an integer from 0 - 2;

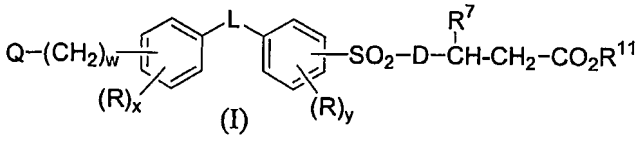
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

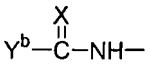
5. The compound of claim 4 having the formula



(I)

wherein

Q is a substituent selected from the group consisting of:

(a) 

wherein

X represents O or N(CN) ;

Y^b represents $-NH_2$, -NH-Y or -Y; and

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_6-C_{10}-aryl,

(a5) C_6-C_{10}-aryl-C_1-C_3-alkyl, and

(a6) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which

contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and $-NZ^1Z^2$; and

(a2) - (a6) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or $-NZ^1Z^2$,

wherein

Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

(b) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(b1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(b2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the

other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(b2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(b2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (b1) - (b2) are optionally substituted by R;

(c) Y^c=N-

wherein Y^c is as defined in (b) above;

(d) Y^dY^e-N-

wherein Y^d and Y^c are independently selected from the group consisting of hydrogen, C_1-C_5-alkyl, and C_1-C_5-aminoalkyl;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1, and

(g) NR^1R^2,

wherein for (f)-(g):

R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

or

wherein for (i):

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) O,

(b) C(=O),

(c) CR^3R^4,

(d) $S(=O)_z$, and

(e) $C(=NR^3)$

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen, and

(2) C_1-C_3-alkoxy;

D represents CH_2;

R^7 represents a substituent selected from the group consisting of:

(a) C_2-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_2-C_5-alkynyl,

where (a)-(f) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (g)-(j) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_nR^{10}$,

(5) NR^8R^9,

(6) OR^8, or

(7) $C(=O)R^{10}$,

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (g) – (j) are substituted by NR^8R^9, ,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl;

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_3-C_5-alkynyl,

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (a)-(j) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl, and

(c) C_3-C_6-cycloalkyl,

wherein (a)-(c) are optionally substituted by:

(1) halogen,

(2) OR^{12}, or

(3) $NR^{12}R^{13}$;

wherein

R^{12} and R^{13} each independently represents hydrogen or C_1-C_3-alkyl;

or

R^{12} and R^{13} together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen

and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

u is an integer from 0 - 2;

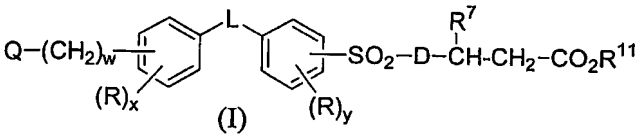
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

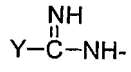
6. The compound of claim 1 having the formula



(I)

wherein

Q is a substituent selected from the group consisting of:

(a) 

wherein

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_3-C_5-alkenyl,

(a5) C_4-C_8-cycloalkenyl,

(a6) C_3-C_5-alkynyl,

(a7) C_6-C_{10}-aryl,

(a8) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(a9) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(a10) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which

contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

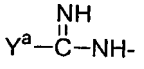
(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and $-NZ^1Z^2$; and

(a2) - (a10) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or $-NZ^1Z^2$, wherein

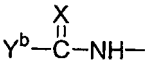
Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

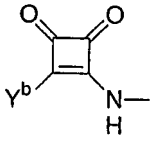
Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

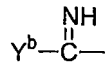
(b) 

wherein Y^a represents $-NH_2$ or -NH-Y;

(c) 

wherein X represents O or N(CN) ;

(d)  ;

(e) 

wherein for (c) - (e)

Y^b represents $-NH_2$, -NH-Y or -Y;

(f) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(f1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(f2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(f2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(f2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (f1) - (f2) are optionally substituted by R;

(g) Y^c=N-

wherein Y^c is as defined in (f) above;

(h) Y^dY^e-N-

wherein Y^d and Y^e are independently selected from the group consisting of hydrogen, C_1-C_5-alkyl, and C_1-C_5-aminoalkyl;

and

(i) when w = 0, Q forms a four to eight membered heterocyclic ring fused to the aryl group to which it is attached to form a bicyclic ring, wherein said heterocyclic ring contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and at least one carbon atom and said heterocyclic ring is optionally substituted with C_1-C_5-alkyl or $-NZ^3Z^4$ wherein Z^3 and Z^4 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl;

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1,

(g) $C(=O)OR^1$,

(h) $S(=O)_2OR^1$,

(i) NR^1R^2,

(j) $C(=O)NR^1R^2$, and

(k) $S(=O)_2NR^1R^2$;

wherein for (f)-(k):

R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

or

wherein for (i)-(k):

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) $C(=O)N(R^5)$,

(b) $N(R^5)C(=O)$,

(c) $S(=O)_2N(R^5)$

(d) $N(R^5)S(=O)_2$,

(e) CR^3R^4-CR^3R^4,

(f) CH_2O,

(g) OCH_2,

(h) $CH_2N(R^5)$,

(i) $N(R^5)CH_2$,

(j) CH=CH, and

(k) -C≡C- ;

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) C_1-C_3-alkyl, and

(4) C_1-C_3-alkoxy;

wherein:

when one or two R^3 groups are C_1-C_3-alkyl in L, said one or two R^3 groups may constitute spiro rings or nonspiro rings wherein:

(a) one group R^3 is joined by a bond or by a heteroatom selected from the group consisting of oxygen, nitrogen and sulfur, to the carbon chain to which said group R^3 is attached, and taken together with the carbon chain atom(s) to which said group R^3 is attached, constitutes a ring of three to six members,

wherein for CR^3R^4, when R^3 is C_1-alkyl, the R^3 group is joined by a heteratom as defined above, or

(b) two groups R^3 are joined by a bond or by a heteroatom selected from the group consisting of oxygen, nitrogen and sulfur and taken together with the carbon chain atom(s) to which said two groups R^3 are attached, constitute a ring of 3-6 members;

R^5 represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

D represents CH_2 ;

R^7 represents a substituent selected from the group consisting of:

(a) C_2-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_2-C_5-alkynyl,

where (a)-(f) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (g)-(j) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,

(2) CN,

(3) halogen,

(4) $S(=O)_2OH$,

(5) $S(=O)_nR^{10}$,

(6) $S(=O)_2NR^8R^9$,

(7) NR^8R^9,

(8) OR^8,

(9) $C(=O)R^{10}$,

(10) $C(=O)OR^8$; or

(11) $C(=O)NR^8R^9$;

wherein:

R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (g) – (j) are substituted by NR^8R^9, $S(=O)_2NR^8R^9$ or $C(=O)NR^8R^9$,

R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen

and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:

(a) C_1-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl;

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_3-C_5-alkynyl,

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (a)-(j) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl,

(c) C_3-C_6-cycloalkyl,

(d) C_3-C_6-alkenyl,

(e) C_5-C_6-cycloalkenyl, and

(f) C_3-C_6-alkynyl

wherein (b)-(f) are optionally substituted by:

(1) halogen,

(2) OR^{12}, or

(3) $NR^{12}R^{13}$;

wherein

R^{12} and R^{13} each independently represents hydrogen or C_1-C_3-alkyl;

or

R^{12} and R^{13} together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

u is an integer from 0 - 2;

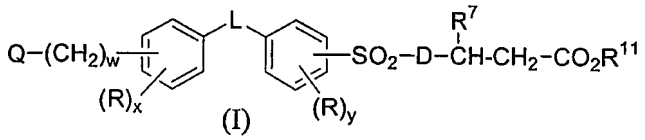
v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

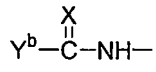
7. The compound of claim 6 having the formula



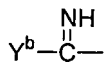
(I)

wherein

Q is a substituent selected from the group consisting of:

(a) 

wherein X represents O or N(CN) ;

(b) 

wherein for (a) and (b),

Y^b represents $-NH_2$, -NH-Y or -Y; and

Y is selected from the group consisting of:

(a1) C_1-C_5-alkyl,

(a2) C_3-C_8-cycloalkyl,

(a3) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(a4) C_6-C_{10}-aryl,

(a5) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(a6) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(a7) $(CH_2)_a$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein:

(a1) is optionally substituted by halogen up to perhalo, or by one to three substitutents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkylthio, C_6-C_{10}-aryl and -NZ^1Z^2; and

(a2) - (a7) are optionally substituted by halogen up to perhalo, or by one to three substituents selected from the group consisting of halogen, cyano, C_1-C_3-alkoxy, C_1-C_3-alkyl, C_1-C_3-alkylthio, C_6-C_{10}-aryl or -NZ^1Z^2,

wherein

Z^1 and Z^2 are independently selected from the group consisting of hydrogen and C_1-C_5-alkyl,

or

Z^1 and Z^2 may be joined by a chemical bond or by an N, O, or S heteroatom, and taken together with the nitrogen atom to which they are bound, form a 5-6 membered saturated or unsaturated heterocycle;

(c) Y^c-NH-$(CH_2)_u$-

wherein

Y^c is a heterocycle selected from:

(c1) a five to seven membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom and optionally one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and

(c2) a fused bicyclo ring wherein one ring is a four to eight membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or unsaturated four to eight membered saturated or unsaturated ring which contains zero to four heteroatoms and at least one carbon atom,

wherein:

(c2a) the ring bonded to NH contains a nitrogen atom and optionally contains one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and

(c2b) the ring not bonded to NH contains zero to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein (c1) - (c2) are optionally substituted by R;

(d) Y^c=N-

wherein Y^c is as defined in (c) above;

(e) Y^dY^e-N-

wherein Y^d and Y^e are independently selected from the group consisting of hydrogen, C_1-C_5-alkyl, and C_1-C_5-aminoalkyl;

and

R represents a substituent selected from the group consisting of:

(a) halogen,

(b) C_1-C_4-alkyl, optionally substituted by halogen,

(c) C_6-C_{10}-aryl, optionally substituted by halogen,

(d) NO_2,

(e) CN,

(f) OR^1, and

(g) NR^1R^2,

wherein for (f)-(g):

R^1 and R^2 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

or

wherein for (g):

R^1 and R^2 together with the nitrogen to which they are attached represent a four to eight membered heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said heterocyclic ring contains at least one carbon atom;

L represents a substituent selected from the group consisting of:

(a) CR^3R^4-CR^3R^4,

(b) CH_2O,

(c) OCH_2,

(d) $CH_2N(R^5)$,

(e) $N(R^5)CH_2$,

(f) CH=CH, and

(g) -C≡C- ;

R^3 and R^4 each independently represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) halogen, and

(3) C_1-C_3-alkoxy;

R^5 represents a substituent selected from the group consisting of:

(1) hydrogen,

(2) C_1-C_4-alkyl, optionally substituted by halogen, and

(3) C_3-C_8-cycloalkyl, optionally substituted by halogen;

D represents CH_2 ;

R^7 represents a substituent selected from the group consisting of:

(a) C_2-C_5-alkyl,

(b) C_3-C_8-cycloalkyl,

(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl,

(d) C_3-C_5-alkenyl,

(e) C_4-C_8-cycloalkenyl,

(f) C_2-C_5-alkynyl,

where (a)-(f) are optionally substituted by

(1) OR^8,

(2) NR^8R^9, or

(3) halogen;

(g) C_6-C_{10}-aryl,

(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,

(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and

(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (g)-(j) are optionally substituted by one to three substituents selected from the group consisting of:

(1) NO_2,
(2) CN,
(3) halogen,
(4) $S(=O)_nR^{10}$,
(5) NR^8R^9,
(6) OR^8, and
(7) $C(=O)R^{10}$,
wherein:
R^8 and R^9 are independently hydrogen or R^{10};

or optionally

when (g) – (j) are substituted by NR^8R^9,
R^8 and R^9 together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

R^{10} represents a substituent selected from the group consisting of:
(a) C_1-C_5-alkyl,
(b) C_3-C_8-cycloalkyl,
(c) C_3-C_8-cycloalkyl-C_1-C_3-alkyl;
(d) C_3-C_5-alkenyl,
(e) C_4-C_8-cycloalkenyl,
(f) C_3-C_5-alkynyl,
(g) C_6-C_{10}-aryl,
(h) C_6-C_{10}-aryl-C_1-C_3-alkyl,
(i) C_6-C_{10}-aryl-C_3-C_6-cycloalkyl, and
(j) $(CH_2)_b$-A^2 wherein A^2 is a four to ten membered saturated or unsaturated heterocyclic ring which contains one to four heteroatoms selected from the

group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (a)-(j) are optionally substituted with halogen;

R^{11} represents a substituent selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6-alkyl, and

(c) C_3-C_6-cycloalkyl,

wherein (b)-(c) are optionally substituted by:

(1) halogen,

(2) OR^{12}, or

(3) $NR^{12}R^{13}$;

wherein

R^{12} and R^{13} each independently represents hydrogen or C_1-C_3-alkyl;

or

R^{12} and R^{13} together with the nitrogen to which they are attached represent a four to eight membered saturated or unsaturated heterocyclic ring which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom;

u is an integer from 0 - 2;

v is an integer from 1 - 2;

n, w and z are each independently an integer from 0 - 2;

a, b, x and y are each independently an integer from 0 - 3;

or a purified stereoisomer or stereoisomer mixture of said compound, or a salt of said compound, stereoisomer or stereoisomer mixture.

8. A pharmaceutical composition comprising a compound of claim 1 and at least one additional pharmaceutically acceptable ingredient.

9. A pharmaceutical composition comprising a compound of claim 2 and at least one additional pharmaceutically acceptable ingredient.

10. A pharmaceutical composition comprising a compound of claim 4 and at least one additional pharmaceutically acceptable ingredient.

11. A pharmaceutical composition comprising a compound of claim 6 and at least one additional pharmaceutically acceptable ingredient.

12. A method for treating a disease or condition associated with the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ receptor(s), which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1.

13. The method of claim 12 wherein the disease or condition treated is selected from the group consisting of angiogenesis, arteriosclerosis, cancer, diabetic retinopathy, inflammation, macular degeneration, ophthamia, osteoporosis, restenosis, viral disease, and conditions related to inhibition of bone resorption.

14. The method of claim 13 wherein said disease or condition is selected from the group consisting of angiogenesis, cancer, osteoporosis, restenosis, and diabetic retinopathy.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/41692

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C317/32 A61K31/10 A61P19/10 A61P31/12 A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 843 906 A (DOUBLEDAY WENDELL ET AL) 1 December 1998 (1998-12-01) column 34, 3rd - 6th compound from the top column 1, line 15 - line 57	1-14
A	WO 97 36861 A (DOUBLEDAY WENDELL ;CLARE MICHAEL (US); SEARLE & CO (US); GASIECKI) 9 October 1997 (1997-10-09) page 47, compound shown page 1, line 22 -page 2, line 16	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2003	06/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kleidernigg, O

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 02/41692

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 12-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/41692

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5843906 A	01-12-1998	AT 203515 T	15-08-2001
		AU 2420897 A	22-10-1997
		CA 2250586 A1	09-10-1997
		DE 69705829 D1	30-08-2001
		DE 69705829 T2	04-04-2002
		DK 889876 T3	24-09-2001
		EP 0889876 A1	13-01-1999
		ES 2160949 T3	16-11-2001
		GR 3036887 T3	31-01-2002
		JP 2000507952 T	27-06-2000
		PT 889876 T	30-11-2001
		WO 9736861 A1	09-10-1997
WO 9736861 A	09-10-1997	AT 203515 T	15-08-2001
		AU 2420897 A	22-10-1997
		CA 2250586 A1	09-10-1997
		DE 69705829 D1	30-08-2001
		DE 69705829 T2	04-04-2002
		DK 889876 T3	24-09-2001
		EP 0889876 A1	13-01-1999
		ES 2160949 T3	16-11-2001
		GR 3036887 T3	31-01-2002
		JP 2000507952 T	27-06-2000
		PT 889876 T	30-11-2001
		WO 9736861 A1	09-10-1997
		US 5843906 A	01-12-1998